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AUSTRALASIAN ANNALS OF MEDICINE

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GROUNDEDLY LEARNED

THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS, founded in 1938, has this year come of age. It is said, and with a good deal of truth, that it was modelled on the Royal College of Physicians of London. It is often forgotten, however, that the London College was itself fashioned on other and older colleges on the Continent. One was the College of Physicians of Rome, established in the early Middle Ages. This College consisted of twelve Fellows of good family and education who had a large measure of control over local medical practice. There were also the Germanic guilds, powerful corporations of physicians and apothecaries, with wide powers and with exclusive rights of practice. Practitioners could be admitted only after examination by four consuls similar to the censors of later colleges. In all these colleges and guilds, ceremonial was considered important and was associated with dinners, festivities and religious ritual. Later many colleges of physicians were founded in Italy and, indeed, throughout Europe.

The London College was founded on the Italian model, probably as a result of the experiences in Italy of Thomas Linacre. At its founding in 1518 it had six Foundation Fellows, and soon after two others were added, forming the eight first "elects". How rapidly did the College grow? It is not easy to be certain, because the early records of the College are perhaps not very reliable; but according to Munk's Roll, in the first 21 years only 26 Fellows, including the original eight elects, were created. We know that in 1746, over two centuries later, there were only 54 Fellows and 24 licentiates, and in the 60 years between 1760 and 1820 only 128 Fellows and 416 licentiates. During the first 21 years of the College we know the names of only three presidents: Thomas Linacre, 1518–1524; Thomas Bentley, 1526, 1529, 1530; and Richard Bartlot, 1527, 1528, 1531. The gaps in the records extend to the year 1541. All the early Fellows were graduates of Oxford or Cambridge or were incorporated in those Universities, and many had studied on the Continent and possessed foreign medical degrees.

The first building owned by the College was a house which belonged to Linacre. It was occupied for nearly 100 years. The College had three subsequent homes: the Amen Corner residence (1614–1674); the Warwick Lane House (1674–1825); and the present home in Pall Mall. The College now proposes to move once more to its fifth home.

It is of interest now to consider briefly the early days of the Royal College of Physicians of Edinburgh. It received its charter on November 29, 1681, against great opposition from the surgeons, the Town Council, the Universities and the bishops. The College consisted of 21 Foundation Fellows. They had authority to elect further Fellows from within the City of Edinburgh. To placate the Universities, the College undertook not to open a medical school, and all graduates of the Universities might claim to be licensed by the College without examination and without fee.

Of the original 21 Fellows, at least 14 had continental degrees, nine from Leyden and one each from Utrecht, Padua, Rheims, Montpellier and Caen. There is insufficient information about the other seven. It must be remembered that at that time a degree

of doctor of medicine could be obtained in Great Britain only at Oxford or Cambridge or from the Archbishop of Canterbury, who in 1531, by an Act of Parliament, was empowered to give degrees in medicine. Occasionally M.D. degrees were conferred by the King as a sign of royal favour.

In its first 21 years, the Edinburgh College had seven Presidents. Its second President, Sir Robert Sibbald, was made an Honorary Fellow of the London College in 1686. (Honorary fellowships had been established in the London College in 1664, and one of the first recipients was Sir Thomas Browne.) In the early days the Fellows met in each other's houses, but in 1704 the College acquired the first building of its own in Foundation Close. In 1781 it moved to George Street, and in 1846 to its present site.

Both Colleges were founded by men of great distinction, not only in medicine, but also in the humanities. In the original charter of the London College are these words:

> And forasmuch that the making of the said corporation is meritorious and very good for the commonwealth of this your realm, it is therefore expedient and necessary to provide, That no person of the said politic body and commonalty aforesaid be suffered to exercise and practise physic, but only those persons that be profound, sad and discreet, groundedly learned, and deeply studied in physic.

One has only to read the early biographies in Munk's Roll to realize what profound scholars the early Fellows were. Their reputation for general scholarship has tended to give the impression that, although deeply learned in the classics, they were not good physicians. All the evidence suggests that they were regarded as among the very best clinicians of their time, and in subsequent centuries nearly all the great men of British medicine were proud to be Fellows of the College.

The Fellows of both Colleges had control of the practice of medicine in their immediate vicinities, and power to inspect the shops of apothecaries and destroy drugs which they considered "defective or corrupt".

Both Colleges were active in teaching. In London the Lumleian Lecture, founded in 1582, was to be read "in the College every Wednesday and Friday for ever by a Doctor of Physick and fellow of that Colledge". William Harvey was a Lumleian Lecturer from 1615 to 1657. In the early days of the Edinburgh College the fellows met regularly every month for discourses on "all facets of medicine". These meetings were held at irregular intervals up to 1712.

It might be said, then, that these older Colleges were based, firstly on a background of learning with a profound knowledge of the classics and humanities, secondly on a lively and enthusiastic pursuit of the knowledge of medicine, and thirdly on a high ethical standard. They had their faults. They were exclusive, in some ways conservative, snobbish and authoritarian. Until early in the nineteenth century only graduates of Oxford and Cambridge could become Fellows of the London College, and their disdainful treatment of licentiates resulted in 1767 in the latter's breaking into College meetings by force; but on the whole they preserved the best things in the British tradition of medicine.

Let us now look at our own College. What has been accomplished? Our founders started with the whole background of the older colleges—the division into Fellows and Members, the president, the censors, the treasurer, academic gowns and Tudor hats, ceremony and some pageantry. This perhaps sounds a little strange in these new, vigorous, democratic lands. On the whole, however, it has helped to remind Australians and New Zealanders of the long tradition which lies behind our profession. Both the London and Edinburgh Colleges and also the much younger American College of Physicians were represented at our opening ceremonies.

After 21 years, the Australasian College has 357 Fellows and 578 Members. The present President is the eleventh. There are 13 Honorary Fellows, all men of great distinction. The College is well housed in an old colonial home. It has been able to foster much research, and has sent its scholars and Fellows in search of knowledge and experience. It has held regular scientific meetings in the Commonwealth and in the Dominion.

The question is sometimes raised whether a College such as ours continues to have a real value and purpose under the conditions in which medicine finds itself today. In the past, colleges of physicians have disappeared. Where are the many colleges which at one time were scattered over Europe? Few, if any, remain. Yet new colleges continue to be formed, and many believe that their original functions still remain and are of paramount importance.

The older colleges held that it was important for a physician to be "groundedly learned", and behind the apparent exclusiveness of the London College in electing to fellowship only graduates of Oxford and Cambridge was the feeling that these physicians were at least well educated. In the seventeenth century at Oxford it took 14 years to get a medical doctorate, seven years for the preliminary M.A. degree and seven years for the M.D. degree. No wonder so few qualified. We cannot expect today's candidates for the membership to be learned Greek and Latin scholars, but we can demand that they be informed about the great traditions of classical medicine and philosophy, and that they know a great deal of the history of medicine and the history of ideas and have interests and accomplishments outside the purely technical aspects of their profession. What it is to be "groundedly learned" today will always be a matter for difference of opinion; but most people will recognize the difference between the technical scientist and the true physician. Our physicians may not, like Linacre and John Chambre, take holy orders; but we still believe that the quality of the man who practises medicine is of primary importance.

Perhaps the greatest contribution of The Royal Australasian College of Physicians has been the less tangible one—the bringing together of physicians and scientists both in New Zealand and in Australia and imbuing them with a new spirit of freindship, cooperation and enthusiasm. This intercourse has meant a great deal to both countries. The College has been a meeting place for physicians of all age groups. It is well to remember that institutions can be destroyed by the conservatism and rigidity of the old or by the intolerance and iconoclasm of the young.

The history of older colleges should teach us that we must be vigilant to see that, while holding firmly to the fundamental principles on which our profession is founded, we keep our policy flexible enough to meet the new changes in outlook which will inevitably occur. We are still laying the foundations for those who will come after us.

When on December 13, 1642, Abel Tasman first sighted the coast of New Zealand, "a large, high-lying land", the President of the Royal College of Physicians of London was one Othowell Meverall. Munk, describing his life and accomplishments, writes: "He bequeathed to the College, by will, the sum of £40 and to Fellows a gold ring on which was engraved: '*Medici morimur, medicina perennis*'. We doctors die, but medicine is eternal."

E. G. SAYERS.

HÆMOLYTIC DISEASE OF THE NEW-BORN

AN ANALYSIS OF FAMILY HISTORIES AND SEROLOGICAL FINDINGS[1]

R. J. WALSH[2] and H. K. WARD[3]

From the New South Wales Red Cross Blood Transfusion Service, Sydney

SUMMARY

The fate of the infants of 395 immunized Rh-negative women has been analysed.

The severity of the disease in the first affected child frequently sets the pattern for subsequent children. If the first affected child is mildly affected, the subsequent children are more likely to survive than to die; and first-born severely affected children are likely to be followed by stillbirths or fatally affected children. The parity of the mother when the first affected child is born is not related to the chances of survival of the infant. The severity of the disease increases as the mean titre of the incomplete antibody in the maternal serum rises, but there are numerous exceptions to the general rule. The effects of immunization by a blood transfusion are similar to those when immunization follows a pregnancy. The frequency of stillbirths is not significantly greater when immunization follows transfusions.

The significance of these findings is discussed.

IMMUNIZATION of Rh-negative women during pregnancy, with the consequent production of hæmolytic disease in the Rh-positive infant, is relatively rare. Fortunately, most Rh-negative women married to Rh-positive men escape this hazard. Therapy with exchange transfusions of Rh-negative blood has undoubtedly reduced the mortality amongst live-born affected infants, and has probably also reduced the incidence of the cerebral damage known as kernicterus. However, fœtal wastage due to intrauterine death is still an unsolved problem, in spite of early induction of labour in selected instances.

The woman who has produced an affected infant is naturally interested in the likely outcome of future pregnancies, and frequently seeks help from her medical adviser. An accurate prognosis is possible in any disease only if the pathogenesis is fully understood. Much has been learnt about hæmolytic disease of the newborn since the role of maternal immunization by Rh antigens was so convincingly demonstrated by Levine and his colleagues (1941); but it cannot be claimed that the pathogenesis has been completely elucidated. Many questions remain unanswered.

Is the mother immunized by fœtal red cells passing the placenta, or by break-down products of red cells containing the Rh antigens? Do fœtal blood-group antigens cross the placenta in every pregnancy, or must some placental defect occur to permit this passage? Is an immunized Rh-negative woman reimmunized during subsequent pregnancies with Rh-positive infants, or are these infants affected by Rh antibodies which remain in the mother's blood after the initial immunization? Does the mother receive fœtal blood when the placenta separates during parturition, and is this the explanation of the higher incidence of hæmolytic disease of the newborn in second-born Rh-positive infants than in the first-born? What host factors determine immunization of Rh-negative women? What factors determine the apparently variable effect of Rh antibodies on the red cells and tissues of the fœtus in utero and of the infant in the neonatal period? What is the nature of the cerebral damage in some affected infants?

The prognosis for individual patients must be based on probabilities until answers can be given to the foregoing and other questions. We have recently examined the histories and serological findings of immunized Rh-negative women in an attempt to obtain further information concerning the natural history of the disease.

The information obtained in this survey was analysed from the following points of view: (i) the family pattern in hæmolytic disease; (ii) the parity of the mother in relation to the severity of the disease; (iii) the influence of blood transfusion on hæmolytic disease; (iv) the relation of the severity of the disease to the titre of the incomplete Rh antibody.

[1] Received on February 2, 1959.

[2] Director.

[3] Medical Officer.

MATERIALS AND METHODS

The material used was that obtained in the course of an investigation of the persistence of Rh antibodies without antigenic stimulus (Ward, 1957). Women whose blood had been found to contain Rh antibodies in the course of pre-natal investigations were asked to visit the New South Wales Red Cross Transfusion Service, or, if resident in the country, their own medical practitioners. A sample of blood was collected for antibody titration, and a history of pregnancies, including miscarriages, and of transfusions was obtained from each patient.

The severity of hæmolytic disease in affected children has been graded into four categories: (i) mild disease—infant not given a transfusion; (ii) severe disease—infant given a transfusion and survived; (iii) severe disease—infant given a transfusion, but died; (iv) infant still-born. This classification provides a means of comparison, but is arbitrary, and ignores the influence of therapy on the fate of the child. Moreover, the decision to give a transfusion to an affected child varies from hospital to hospital and from one medical practitioner to another.

Titres of the complete antibody were measured against D-positive red cells suspended in physiological saline solution, and titres of the incomplete antibody against D-positive red cells suspended in 10% polyvidone solution. Details of these techniques have been described by Ward (1957).

RESULTS

The Family Pattern in Hæmolytic Disease

Is the severity of the disease in the first affected child of prognostic value for future children? This question was investigated in two ways.

1. The disease in the first affected child was classified into the four grades described above. The fate of the next child in each category was similarly graded, with the results shown in Table I. A total of 395 immunized women were investigated; but of these, 175 had not had a further pregnancy at the time of the examination. The following points may be seen from Table I: (*a*) The percentage of unaffected children was 14·1. This is consistent with the findings of other workers, and with the statement that approximately 25% of the husbands of immunized Rh-negative women are heterozygous in respect of the D antigen—i.e., they are Dd (Mollison, Mourant and Race, 1954), so that 50% of their children will be Rh-negative. (*b*) If the first affected child survives, the next affected child is more likely to survive than to die or to be still-born ($\chi^2=20{\cdot}62$ for 1 degree of freedom; $P<0{\cdot}001$). (*c*) If the first affected child dies, the next Rh-positive child is more likely to die than to survive. (*d*) There are notable exceptions to the last two statements.

These points are shown diagrammatically in Figure 1, which gives the general trend of the family pattern, but at the same time emphasizes the fact that exceptions are frequent.

The same analysis was made of all children born of these immunized women, which enabled the fate of a further 166 infants to be included. The results follow the same pattern as seen in Table I.

2. The severity of the disease in the pregnancies following immunization was investigated by determining the mortality amongst the first affected children, the second affected children, and so on. It was found that 34·2% of the first, 49·4% of the second, 51·3% of

TABLE I

The Fate of the First Affected and the Next Child

First Affected Child	Next Child					
	Not Affected	Mildly Affected	Severely Affected, but Recovered	Severely Affected and Died	Still-born	Total
Mildly affected (115—29·1%)	11 (19·6%)	14 (25·0%)	17 (30·4%)	8 (14·3%)	6 (10·7%)	56
Severely affected, but recovered (145—36·7%)	9 (15·2%)	8 (13·6%)	22 (37·3%)	8 (13·6%)	12 (20·3%)	59
Severely affected and died (62—15·7%)	3 (6·1%)	1 (2·0%)	17 (34·7%)	8 (16·3%)	20 (40·8%)	49
Still-born (73—18·5%) ..	8 (14·3%)	6 (10·7%)	7 (12·5%)	10 (17·9%)	25 (44·6%)	56
Total (395—100%) ..	31 (14·1%)	29 (13·2%)	63 (28·6%)	34 (15·5%)	63 (28·6%)	220[1] (100%)

[1] 175 of the immunized mothers had not had a further pregnancy at the time of examination.

the third and 45·7% of the fourth affected children died. There is, therefore, no progressive increase in mortality. The family pattern thus gives some help in prognosis, in that the mildness or severity of the disease tends to be repeated in succeeding pregnancies.

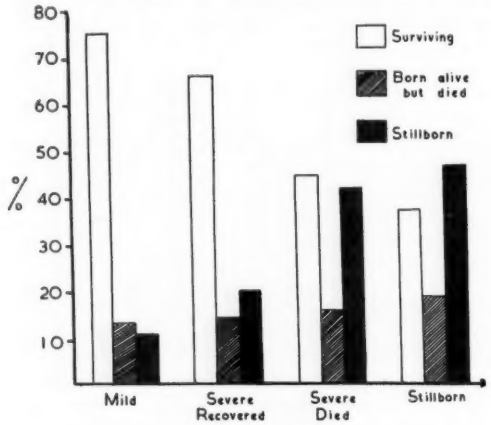

FIGURE I

The severity of the disease in the first affected children is shown by the gradings on the abscissa. The heights of the columns indicate the percentage of the next infants in the families who (*a*) survived, (*b*) were born alive but died, and (*c*) were still-born

Parity of the Mother and Severity of the Disease

The parity of the mother and the severity of the disease in the first affected child are shown in Table II. The percentage of infants surviving is not related to maternal parity ($\chi^2=7·5$ for 4 degrees of freedom; $0·2>P>0·1$). There is, however, a high percentage of still births amongst the affected infants of primiparous women (44·2%), and this differs significantly from the percentage (17·9) when the first affected child is born from the second pregnancy ($\chi^2=9·50$ for one degree of freedom; $0·01>P>0·001$). The series shown in Table II does not contain any mother who, on being directly questioned, stated that she had received a transfusion at some time; but it is possible that some of the primiparous mothers had received intramuscular injections or even transfusions of blood in their own infancy and were unaware of this. Levine and Waller (1946) have suggested this possibility to explain the occurrence of hæmolytic disease in the first-born infant.

TABLE II

The Relation between Parity of the Mother when the First Affected Child was Born and the Severity of the Disease in the Child

Severity in First Affected Child	Parity of the Mother				
	1	2	3	4	5
Mildly affected ..	11	53	30	12	4
Severely affected, but recovered ..	9	78	34	14	5
Severely affected and died ..	0	43	11	9	0
Still-born	14	38	10	9	2
Total	34	212	85	44	11
Percentage surviving	58·8	61·8	75·3	59·1	81·8
Percentage still-born	41·2	17·9	11·8	20·5	18·2

TABLE III

Influence of Previous Transfusion on the Severity of the Disease

Severity in the First Affected Child	Mother Given Transfusion	Mother Not Given Transfusion
Mild	24 (30·4%)	115 (29·1%)
Severe, but child recovered	20 (25·3%)	145 (36·7%)
Severe, and child died	18 (22·8%)	62 (15·7%)
Child still-born	17 (21·5%)	73 (18·5%)
Total	79 (100·0%)	395 (100·0%)

Blood Transfusions and Hæmolytic Disease

It was not possible from our records to determine whether the disease occurs in every Rh-positive infant whose Rh-negative mother has previously received a transfusion of Rh-positive blood. This information could be

TABLE IV

Influence of Titre of Maternal Incomplete Antibodies on the Severity of the Disease in the Child

Severity of Disease in Last Affected Child	Number of Mothers with Titres of													Mean Titre	Mean Interval between Birth of Child and Examination of Serum
	0	2	4	8	16	32	64	128	256	512	1024	2048	4096		
Mild	8	8	16	11	3	7	23	20	16	11	3	0	0	137	33 months
Severe, but child recovered	9	6	12	4	9	5	27	27	49	34	17	5	2	346	34 months
Severe, and child died	1	1	1	2	1	3	5	8	14	12	14	5	0	534	36 months
Child still-born ..	1	1	2	1	2	0	2	12	27	22	19	6	5	790	33 months

obtained only by following all Rh-negative women who had been given such transfusions.

In the present series, the histories of those immunized women who had received transfusions were compared with those who were not aware of any transfusion. Some had certainly received Rh-positive blood, but in the majority of instances the Rh type of the blood was not known. The severity of hæmolytic disease in the first affected infants is shown in Table III. The mortality was slightly greater in the series in which transfusions had been given (44·3% compared with 34·2%), but the difference was not significant ($\chi^2=6\cdot04$ for 3 degrees of freedom; $0\cdot2>P>0\cdot1$).

higher values would have been recorded in the early post-partum periods. However, only the incomplete antibody has been considered, and as the titre of this antibody falls slowly (Ward, 1957), the range of titres is probably similar to that which would have been found in the early post-partum periods.

The Complete Rh Antibody

In this survey the complete antibody was also titrated, but there was no correlation between the titre and the severity of the disease. This is not surprising, as the complete antibody does not pass the placenta into the circulation of the child.

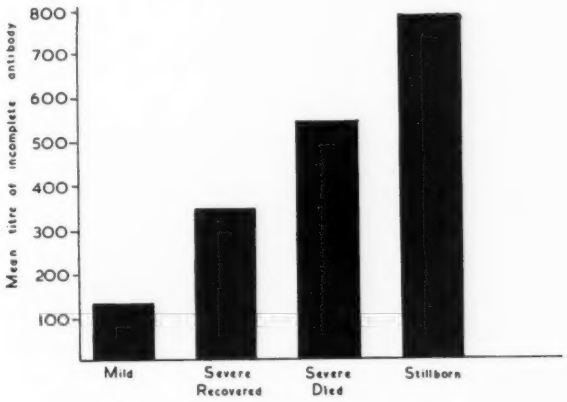

FIGURE II

The relationship between maternal titre of Rh agglutinins and the severity of the disease in the last affected child

Titre of Antibody and Severity of Disease

The severity of the disease in the last affected child and the mean titres of the incomplete antibody are shown in Table IV. The interval between the last affected child and the collection of the mother's serum was noted in every instance (Ward, 1957), and it was found that the mean intervals were comparable in the four groups. It can be seen from Table IV and Figure II that there is a progressive increase in the mean titre with increasing severity of the disease in the infants. There are, however, many exceptions to this general picture. For example, 30 mildly affected infants were associated with maternal titres of 256 or more, and five infants were still-born though the titres were less than 16. It must be pointed out that the titres shown were found at varying intervals after the birth of the infants, and that

DISCUSSION

In the past, it has been taught that the severity of hæmolytic disease in infants usually increases as the number of pregnancies increases, but our own survey does not support this theory. Walker and Murray (1956) were the first to show that "family patterns" often occur, and that the severity of the disease in the first affected child is sometimes a guide to the probable severity in subsequent infants. This has been confirmed by the findings reported in this paper. Although there are many exceptions, a mildly affected infant is more likely to be followed by infants who survive than by infants who die. The reverse also holds; when the first affected infant dies or is still-born, further infants are likely to be similarly affected.

The parity of the mother when the first affected child is born appears to be unrelated to the percentage of infants surviving.

Our findings concerning the general relationship between increasing Rh-antibody titre and increasing severity of the disease in the infant (Figure II) are in agreement with those of most other workers. Although Mollison and Cutbush (1949) found a poor correlation between the titre of the maternal serum 24 hours after the birth of the infant and the degree of anæmia in the infant, they also noted that the mortality rate amongst infants was 21% when the Rh titre was 64 or less, but was 69% when the titre was 128 or more. Nevertheless, exceptions were frequent, and they thought that antibody tests could be used only to forecast probabilities. Wiener and Wexler (1951) showed that in general the percentage of still births increased as the titre of the maternal Rh antibody increased; but they believed that no absolute statement could be made regarding prognosis for a particular infant based on the titre alone. Ponder, Ponder and Levine (1948), from a study of 15 infants with hæmolytic disease, concluded that " . . . if one were to base one's prediction of the severity of the disease on the expectation that a low titer of maternal antibodies would be associated with hemolytic disease in a mild form and that a high titer would be associated with the disease in a severe form, one would be right only 9 times out of 15 ".

On the other hand, Kelsall and Vos (1952) claimed that they could accurately forecast the severity of the disease in the infant from the titre of the maternal antibody when this was determined by a standardized indirect Coombs method. Kirk, Vos and Kelsall (1958) claimed that, when determined by their method, a titre at term of 1/64 or less is of no practical importance; but they give exchange transfusions to all infants when the maternal agglutinin titre is 1/128 or more. Our results and those of other workers cited above do not agree with the absolute statement of Kirk and his colleagues. It is possible that the discrepancy is due to the different techniques used for antibody measurement. However, the pathogenesis of hæmolytic disease almost certainly involves a number of factors, and it would be surprising if the severity of the disease depended solely on the titre of the maternal antibody, important though the titre may be.

Vos (1958) has now proposed a further test, termed the " partial absorption (PA) " test, in which a measured quantity of the maternal serum is absorbed with an equal volume of a 25% suspension of washed Rh-positive cells which have been hæmolysed by freezing. The remaining agglutinin is then titrated by the indirect Coombs method, and the result termed the " PA " titre. In some instances there is little difference between the unabsorbed and the absorbed titres of the maternal serum, but in other cases the absorbed titre is much lower. This would mean that there are two kinds of Rh antibody, differing in their combining capacity for Rh antigens. This is an interesting hypothesis, but it needs further investigation.

Kirk, Vos and Kelsall (1958) claim that the " PA " titre is related to the free Rh antibody in the infant's serum, and is even more reliable as a prognostic guide than the unabsorbed titre of the maternal serum. We are unable to comment on this claim, as we have had no experience with the " PA " test.

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ACUTE INTERMITTENT PORPHYRIA

A FAMILY STUDY[1]

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SUMMARY

A family in which 11 cases of acute intermittent porphyria were found in three consecutive generations has been studied. Evidence is presented that inheritance was by an autosomal dominant gene.

The usefulness of the Watson and Schwartz test in such a study and in the diagnosis of acute cases is discussed. It is suggested that it be applied to all relatives of known acute porphyrics.

The disease as seen in this family is identical clinically, genetically and biochemically with that found in Sweden, and quite distinct from porphyria cutanea tarda.

THE classification of the porphyrias presented by Waldenström (1957) is probably the most useful (Rimington, 1958*a*). This is shown in Table I, together with the changes in excretion of porphyrins and porphobilinogen found in each condition. Congenital porphyria is considered to be transmitted as a recessive character (Waldenström, 1957) and porphyria cutanea tarda hereditaria as a dominant one (Holti *et alii*, 1958). Waldenström (1937, 1956), after extensive studies in Sweden, concluded that acute intermittent porphyria in that country was inherited as a non-sex-linked dominant. Although numerous other instances of the occurrence of this type of porphyria in more than one member of a family have been reported, no study as complete as the Swedish one has been published. Hence the mode of inheritance outside Sweden is less certainly established.

Thirteen cases of acute intermittent porphyria have been reported in Australia. In none was a complete family survey undertaken. Derrick (1946) found that the mother of one of his two patients was affected; Hetzel (1949) recorded no investigation of the relatives of his patients; and in only three of the nine cases reported by Saint and his colleagues (Saint *et alii*, 1952; Saint *et alii*, 1954) were other members of the families found to be affected.

The present study was prompted by the death in 1957 of a woman, aged 27 years, from acute intermittent porphyria. It was subsequently found that her father excreted significant amounts of porphobilinogen.

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TABLE I

The Porphyrias, Classified According to Waldenström (1957); the Abnormal Excretions of Porphobilinogen and Porphyrins Generally Found

Condition	Urine			Fæces		
	Porphobilinogen	Uroporphyrin	Coproporphyrin	Uroporphyrin	Coproporphyrin	Protoporphyrin
Congenital porphyria:						
Attack	−	+++	+	±	++	−
Remission	−	+	+	±	+	−
Porphyria cutanea tarda symptomatica—(i) alcoholic cirrhosis, (ii) Bantu cirrhosis, (iii) exceptional cases:						
Attack	±	+++	++	+	−	−
Remission	−	+	±	−	++	++
Porphyria cutanea tarda hereditaria:						
Attack	±	+++	++	+	−	−
Remission	−	+	±	−	++	++
Acute intermittent porphyria:						
Attack	+++	+++	+	+	+	−
Remission	+	+	±	−	−	−

METHODS

Collection of Material

Each family group was personally visited, and a medical history of each person was obtained. Collection of 24 hour urine specimens was impracticable. Instead, evening urine was pooled with that passed next morning in a bottle containing five grammes of sodium carbonate. It was collected the same morning and tested for porphobilinogen. At the same time specimens of fæces were obtained from 36 members of the family. Both urine and fæces were stored at −20° C., and quantitative porphyrin estimations were made two to four days later.

Estimation of Porphyrins

Urine.—(*a*) Porphobilinogen: the qualitative test of Watson and Schwartz (1941) was performed on all urine specimens when fresh.

TABLE II

Biochemical and Clinical Data

Case Number	Age (Yrs.)	Sex	Urine			Fæces		Clinical Features	Diagnosis
			Porphobilinogen	Uroporphyrin (µg. per 100 ml.)	Coproporphyrin (µg. per 100 ml.)	Protoporphyrin (µg. per Gramme Dry Weight)	Coproporphyrin (µg. per Gramme Dry Weight)		
Normal values				0–5	2–15	0–30	0–20		
1	55	F.						Died at 55 years, "stroke"	Undetermined
2	70	M.						Died at 70 years, cause unknown	Undetermined
3	72	F.						Died at 72 years from carcinoma of the uterus with metastases. Suffered periodic attacks of abdominal pain. Urine stained bedclothes dark pink	Undetermined
4	47	F.						Died at 47 years, cause unknown	Undetermined
5	74	M.						Died at 74 years, "heart disease"	Undetermined
6	22	M.						Died at 22 years, war injuries	Undetermined
7	72	M.						Died at 72 years, cause unknown	Undetermined
8	69	M.	+	83	26	20	21	Symptomless	Latent porphyria
9	54	F.	+	61	52	14	18	Suffers from pains in back and shoulders. Urine often dark and stains clothes dark pink colour. No acute attacks	Acute porphyria (mild)
10	42	F.	−	0	9	17	16	Symptomless	Normal
11	46	F.	+	25	13	4	22	25 years' chronic constipation, attacks of abdominal pain and vomiting. Severe attack in 1957—laparotomy performed for suspected bowel obstruction	Acute porphyria (severe)
12	—	F.	+	54	12			In U.S.A.; analyses by First Army Hospital Laboratory, New York	Latent porphyria
13	20	F.						Died 2 days after abortion when 5 months pregnant, at age of 20 years, cause unknown	Undetermined
14	44	M.	+	40	31	5	13	20 years' right-sided abdominal pain. Urine often dark in colour. Cholecystogram and intravenous pyelogram normal	Acute porphyria (mild)
15	40	M.	+	230	32	10	3	Symptomless	Latent porphyria
16	36	M.	+	160	79	4	4	Symptomless	Latent porphyria
17	39	F.	+					Acute attack with abdominal pain, muscular paralyses and altered consciousness when aged 19 years. Thereafter general health poor. Urine contained porphobilinogen in 1952. Died from hypertensive heart disease at 39 years in 1955	Acute porphyria (severe)
18	44	M.	−	0	3	3	4	Symptomless	Normal
19	3	F.						Died at 3 years, diphtheria	Undetermined
20	40	F.	+	246	6	30	49	Symptomless	Latent porphyria
21	38	F.	−	0	3	26	15	Symptomless	Normal
22	34	M.	−	5	10			Symptomless	Normal
23	27	F.	+	2210	680			Acute attack when 7 weeks pregnant—abdominal pain for 2 weeks, then several convulsions followed by passage of dark urine, altered consciousness, muscular paralysis, absolute constipation and finally abortion and death from respiratory paralysis 26 days after first convulsion. No abnormal symptoms during first pregnancy	Acute porphyria (severe)
24	36	F.	−	2	3	7	7	Symptomless	Normal.
25	10	M.	+	41	8	2	3	Symptomless	Latent porphyria
26 to 54	2 to 26[1]		−	0	1–15	1–23	1–11	Symptomless	Normal

[1] Only four of these individuals were older than 15 years.

(*b*) Uroporphyrin: the method of Sveinsson, Rimington and Barnes (1949) was used. (*c*) Coproporphyrin: the method of Rimington (1958*b*) was used, including the correction equation for impurities of Rimington and Sveinsson (1950).

Fæces.—Coproporphyrin and protoporphyrin were estimated by the method described by Rimington and his colleagues (Holti *et alii*, 1958).

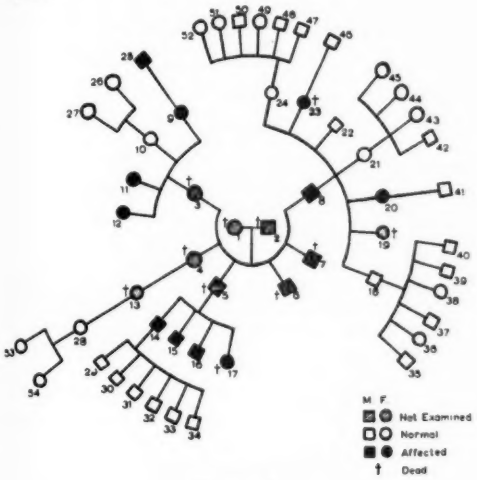

FIGURE I
Pedigree of the family

RESULTS

The results of the chemical and clinical investigation, together with the diagnoses in regard to porphyria, are shown in Table II. Persons designated as "acute porphyria" are those with the clinical and chemical stigmata of acute intermittent porphyria, while "latent porphyria" applies to those members of the family who excrete abnormal quantities of porphobilinogen and porphyrins, but who have no symptoms attributable to porphyria (Waldenström, 1937). "Undetermined" are those members who were unavailable through death. "Normal" indicates those who are symptomless and had normal urinary and fæcal excretion at the time of the investigation.

The pedigree of the family is shown in Figure I.

DISCUSSION

The incidence of porphyria in this family is compatible with inheritance by a non-sex-linked dominant gene. In favour of this are the findings of the disorder in three successive generations, of transmission from father to daughter and mother to son, and of the high incidence in the third generation, nine of 16 individuals in this generation being affected. Of the 11 definite porphyrics, five were male and six female; this indicates the absence of sex linkage. In the fourth and fifth generations, of which only one member was affected, only four persons were older than 15 years. Several authors have noted the low incidence of the biochemical or clinical stigmata of porphyria in children. Waldenström (1956) obtained completely negative results from the examination of the urine of 50 children with one porphyric parent, and concluded: "This inborn error of metabolism does not manifest itself in any way until after puberty." Of his 321 subjects only one was a child—aged 12 years. Hence the low incidence of abnormality in the last two generations of this family does not oppose the conclusion that inheritance is by a dominant gene. Although all the members in the fourth and fifth generations, except one, have been called "normal", this applies only to the results of our relatively crude clinical and biochemical tests. It is probable that some have the genetic abnormality and that this will manifest itself later in life.

The term "latent porphyria" was introduced by Waldenström, who found 20 such cases among 103 persons with acute intermittent porphyria (Waldenström, 1937). Watson (1954*a*) recorded a similar incidence. In the family here presented there were six with latent porphyria out of 11 affected persons. That they are symptomless now does not preclude them from developing symptoms in the future. Waldenström and Vahlquist (1944) reported that several such persons later developed symptoms of an acute attack.

Another unusual type of acute intermittent porphyria is illustrated by the person who intermittently excretes porphobilinogen. Waldenström (1956; Waldenström and Vahlquist, 1944) found several such persons, and others have been reported in the literature. Only frequent reinvestigation of families will reveal such cases. Their incidence is generally found to be low, and in this family all those known to have had acute attacks or to suffer from symptoms suggestive of porphyria showed excessive excretion of porphobilinogen. This suggests a low incidence here, but does not rule out the possibility that there may be people with latent porphyria who excrete porphobilinogen intermittently.

In every case in which porphobilinogen was detected in the urine by the Watson and Schwartz test in this investigation, the urinary porphyrin excretion was also increased. Walden-

ström, in 1937, first showed that excessive excretion of porphobilinogen was characteristic of this disease, and that testing for it was a valuable way of diagnosing acute, quiescent and latent cases. Watson and Schwartz introduced their test in 1941. Since then it has been shown that false positive results are extremely rare. Hammond and Welcker (1948) performed the test on 1000 patients, with negative results in all. Tricomi and Baum (1958) tested urine from 510 pregnant women with similar results, while Watson himself states (1954*b*) that in " several thousand " tests over 15 years there were only 11 false positive results, all in persons suffering from serious diseases. He also states that the result of the test was positive during attacks in all the cases of acute intermittent porphyria that he has studied. It is apparent that a positive response to the Watson and Schwartz test is highly specific for this disease, and our own observations help to show that this simple test is just as valuable for making the diagnosis as estimation of urinary porphyrin excretion.

Considerable confusion regarding the clinical features and classification of porphyria has resulted from the studies of porphyria in the European population of South Africa by Dean and Barnes (1955, 1958). They describe only one condition, inherited as a dominant characteristic, and manifesting itself by skin lesions, as well as by acute attacks indistinguishable from the attacks of acute intermittent porphyria, both clinically and biochemically. They consider that it is a form of acute porphyria quite distinct from that described by Waldenström, who found no skin lesions. It was suggested (Dean and Barnes, 1955) that the occurrence of skin lesions in South Africa and not in Sweden may have been due to the fact that Sweden does not have the year-round sunshine found in South Africa. Later, Dean and Barnes (1958) reported the fæcal as well as urinary excretion of porphyrin and porphobilinogen in quiescent as well as in acute cases. These findings were considered by Rimington (1958) to be characteristic of porphyria cutanea tarda, and it seems more reasonable that the disease in South Africa is a form of porphyria cutanea tarda hereditaria. In our study, fæcal as well as urinary excretion of porphyrin was measured in the majority of cases in the hope of throwing some light on this problem. None of our patients had any skin lesions, even though the annual number of hours of sunshine in Western Australia is probably no less than in South Africa, and several of our patients were dairy farmers, living a great part of their lives out of doors. Further, none of our patients showed more than the slightest increase above normal in fæcal porphyrin excretion, and all, as far as can be ascertained, continued to excrete porphobilinogen in the quiescent stages of their disease. Thus, the disease as seen in this family in Western Australia is exactly as found by Waldenström in Sweden, and quite distinct from porphyria cutanea tarda, according to Rimington's biochemical criteria.

The association of porphyria and pregnancy has often been reported. It is generally held that pregnancy affects porphyria adversely, although this is by no means a constant occurrence (Vannotti, 1954; Vine *et alii*, 1957). Both of the cases described by Hetzel (1949) were in pregnant women, and both patients died. In our study, the only person to die during an attack of acute porphyria was also pregnant (Case XXIII). An important consideration here is the possibility of the administration of drugs, particularly barbiturates, which may precipitate attacks. This woman did not have any barbiturate before the attack commenced. The patient in Case XIII died after a sudden illness when pregnant, although it has been impossible to prove whether or not her death was due to porphyria.

The clinical features of the porphyrias have been frequently described in reviews and case reports and will not be discussed here. It can, however, be pointed out that, although the name " acute intermittent porphyria " is most useful in indicating the intermittent occurrence of acute attacks, it does suggest freedom from symptoms between these attacks. That this is frequently not the case has been pointed out by Vannotti (1954). Several of our cases illustrate this. Thus, in Cases XI and XVI, the patients continued to have symptoms after their acute attacks in a milder, chronic form, while the patients in Cases IX and XIV had mild, recurrent symptoms probably due to the porphyria, although they had never suffered from acute attacks.

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PULMONARY FUNCTION IN PATIENTS WITH A SINGLE FUNCTIONING LUNG[1]

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SUMMARY

Pulmonary function was studied in nine subjects with a loss of functioning lung tissue ; five of these had had a pneumonectomy, one had a large pleural effusion, and three had a pneumothorax. Lung volumes and ventilations and blood gas concentrations were determined, as well as the steady-state physiological dead-space diffusing capacity for carbon monoxide.

After pneumonectomy there tended to be an inflation of the remaining lung, which did not affect any subdivision of lung volume particularly.

Diffusing capacity was reduced after pneumonectomy, but in three cases, only to the lower level of normal for persons with two lungs. In no case was its reduction sufficient to cause lowering of the arterial oxygen saturation, and its reduction did not call for increased ventilation.

The physiological dead space after pneumonectomy was higher than in normal subjects. This necessitated some increase in ventilation.

Diffusing capacity was reduced in pneumothorax, increasing as the lung reexpanded.

In one patient with a pleural effusion, the diffusing capacity was severely reduced.

A NORMAL INDIVIDUAL at rest has a good reserve of pulmonary function, and the loss of function of one lung does not cause embarrassment. After a pneumonectomy, many patients have little limitation of their exercise tolerance. The remaining lung frequently expands to fill part of the contralateral hemithorax and is then described as "over-inflated", this expansion occurring in the first three months after resection (Friend, 1954). However, this "over-inflation" does not seem to cause respiratory insufficiency, and is compatible with many years of life. In the early stages of a spontaneous pneumothorax the patient is usually distressed ; but, if reinflation is delayed, the patient usually improves and is not distressed by light exertion. It is thus of interest to know whether the "normal" lung remaining after successful pneumonectomy, or the lung remaining fully expanded in the case of pneumothorax, is performing more than its previous function, and, if so, to what extent. In particular, the diffusing capacity was studied in these cases in order to see whether it increased beyond what one would expect for a single lung.

The ideal way to study the effect of pneumonectomy on pulmonary function would be to do studies before and after the resection of healthy lungs. In practice, the nearest approach to this is to study patients from whom a lung is removed for a physiologically insignificant lesion. This could be done in only one case, and the other subjects were studied after, but not before, successful pneumonectomies. The other difficulty is that some patients studied pre-operatively were, at operation, found to be unsuitable for study, because of the spread of malignant disease beyond the affected lung.

Patients with a pneumothorax are easier to study, as tests may be performed while the pneumothorax is present, and again after reinflation of the lung.

All symbols and abbreviations used in this paper follow the standard nomenclature (Pappenheimer *et alii*, 1950 ; Comroe *et alii*, 1955) unless otherwise stated.

MATERIAL AND METHODS

Subjects of the Study

Nine patients are included in the present report. Five had had a pneumonectomy ; one of them was studied before and after operation. Only patients whose clinical condition appeared satisfactory after an apparently successful resection are included. Another patient had a very large pleural effusion, while the other three were investigated before and after reinflation of a lung which had collapsed from spontaneous pneumothorax. A summary of the case histories is given below. Physical data and the times of testing are shown in Tables I and II.

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[2] Marion Clare Reddall Research Scholar.
[3] Supported in part by grants from the National Health and Medical Research Council and the Joint Coal Board.

CASE I.—P.S. had a right pneumonectomy for carcinoma on April 9, 1956. Diffusion studies were performed on April 24, when the patient was making satisfactory progress. Estimations of lung volumes, mixing and maximum breathing capacity were performed four months later.

CASE II.—B.M. had a left pneumonectomy for carcinoma in April, 1951. Dyspnœa gradually increased, but he was still very well when first studied in May, 1956. Radiologically, his right lung extended well over into the left hemithorax and clearly had a raised volume (Figure I). In July, 1958, he had an attack of bronchitis, which appeared to precipitate right-sided cardiac failure. He did not recover well from this, and when examined in September he was dyspnœic even when undressing. Physical examination of the patient revealed pulmonary hypertension with cor pulmonale. After two weeks of therapy he was much better subjectively and objectively, and function tests were performed again. The X-ray findings at this time were the same as before. Dyspnœa was much less.

CASE III.—W.S. had a right pneumonectomy for abscess in November, 1955. He felt a little short of breath after the operation, and when studied in May, 1956, he complained of shortness of breath on walking up hills, but otherwise felt well. An X-ray examination of his chest revealed little distension of the left lung.

CASE IV.—R.H. had a left pneumonectomy for carcinoma in December, 1955. He complained that after operation he was much shorter of breath than he had been before, but it is thought that this symptom was somewhat exaggerated. A chest X-ray film taken just before he was studied in August, 1956, showed a little distension of the right lung.

CASE V.—C.F. had a kidney removed for a Grawitz tumour in 1948. In June, 1956, he had a left pneumonectomy for two small secondary deposits. Pulmonary function studies were done a few days prior to operation. He was breathless for some months after the operation, but in September, 1957, he felt well and was not dyspnœic, and function tests were repeated. X-ray examination at this time showed a little distension of the right lung (Figure II).

CASE VI.—L.M. had a large pleural effusion causing almost complete collapse of his left lung. Function tests were carried out, and carcinoma of the left lung was diagnosed by biopsy soon after.

CASE VII.—R.B. had a right spontaneous pneumothorax on March 8, 1955. He was a little breathless for about two days, but improved, and at the time of the studies on March 15 he was not distressed at rest. After the tests, the lung was reexpanded (three litres of air were removed from the pleural cavity), and he was discharged from hospital soon after. He remained in good health, and tests were repeated on June 17, 1955.

CASE VIII.—G.C. was admitted to hospital on July 3, 1956, having had a spontaneous pneumothorax 11 days before. He had been very dyspnœic during this period, and X-ray examination revealed complete collapse of the right lung. Tests were performed on July 5, 1956, and the lung was reinflated. Tests were repeated on July 20, 1956.

CASE IX.—A.W. worked from 1934 to 1940 in a foundry, exposed to silica. He had no evidence of silicosis and was well until an attack of bronchitis in June, 1957. Early in September, he became acutely breathless after a cough, and was found to have a right pneumothorax. The lung was reexpanding when studies were done on October 4. Reexpansion was completed by insertion of an intercostal catheter, and further tests were done on October 10, 1958. An X-ray examination also showed a bulla in the apex of the left lung.

TABLE I

Data Relating to the Five Subjects Studied after Pneumonectomy

Case Number	Patient	Sex	Age (Years)	Height (Inches)	Weight (Pounds)	Surface Area (Square Metres)	Lung Resected	Period between Resection to Studies
I: (*a*)	P.S.	M.	52	68	133	1·72	Right	15 days
(*b*)	P.S.	M.	52	68	133	1·72		4 months
II: (*a*)	B.M.	M.	60	67	151	1·81	Left	5 years
(*b*)	B.M.	M.	63	67	130	1·68		7½ years
III	W.S.	M.	54	67	141	1·76	Right	6 months
IV	R.H.	M.	62	72	163	1·94	Left	8 months
V: (*a*)	C.F.	M.	53	64	123	1·60	Left	Before resection
(*b*)	C.F.	M.	55	64	132	1·65		15 months

TABLE II

Data Relating to One Subject with Pleural Effusion and to Three Subjects with Pneumothorax

Case Number	Patient	Sex	Age (Years)	Height (Inches)	Weight (Pounds)	Surface Area (Square Metres)	Condition
VI	L.M.	M.	62	70	145	1·82	Left pleural effusion
VII: (*a*)	R.B.	M.	30	70	172	1·95	Right lung 72% collapsed[1]
(*b*)	..	..	..	..	..	..	Lung reinflated
VIII: (*a*)	G.C.	M.	61	65	125	1·62	Right lung 90% collapsed[1]
(*b*)	..	..	..	..	..	..	Lung reinflated
IX: (*a*)	A.W.	M.	52	70	114	1·64	Right lung 68% collapsed[1]
(*b*)	..	..	..	..	..	..	Lung reinflated

[1] Estimated by radiological method (see text).

Pulmonary Function Tests

The methods used for pulmonary function tests are substantially the same as those reported previously (Holland and Blacket, 1958). In all resting studies the patient was on a cardiac bed propped up at an angle of 70°–80°, and exercise was on a stationary bicycle ergometer.

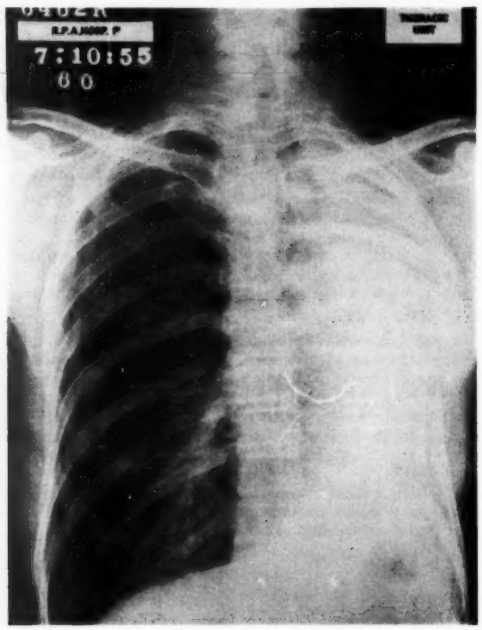

FIGURE I

Postero-anterior chest film of B.M. (Case II), showing the marked overinflation of the remaining lung

The diffusing capacity of the lung for carbon monoxide (D_LCO) was determined by a modification of the method of Filley *et alii* (1954). Carbon monoxide in air was measured by the modification of the spectrophotometric method of Courtice and Gunton (1949) in Case VII (*a*); by the iodine pentoxide method of Adams and Simmons (1951) in Cases I, II (*a*), III, V (*a*) and VII (*b*); and by an infra-red gas analyser in the remainder. Arterial carbon dioxide tension was read from the nomogram of Singer and Hastings (1948). The blood pH was measured by a specially calibrated Cambridge pH meter with the use of an anaerobic cell with a Stadie microelectrode. The blood gas concentrations were determined by the manometric methods of Van Slyke and Neill (1924), and oxygen saturations were corrected for the presence of physically dissolved oxygen. Lung volumes were determined with a six-litre closed-circuit spirometer, helium being used as the indicator gas for the functional residual capacity (F.R.C.) determination. Maximum breathing capacity (M.B.C.) was determined over 12 seconds' breathing on the spirometer.

All values for gas uptake are expressed corrected to "standard temperature and pressure dry" (S.T.P.D.); ventilation, dead space and tidal volume are corrected to body temperature and pressure saturated with water vapour (B.T.P.S.); and lung volumes are expressed at ambient temperature and pressure saturated with water vapour (A.T.P.S.). Lung volumes and M.B.C. were compared with the values predicted for the individual by the formulæ of Needham *et alii* (1954), based on age, sex, height and weight.

A measure of mixing efficiency, as suggested by Colebatch (1958), was obtained from an analysis of the closed-circuit curves of helium concentration. The volume of air required per litre of F.R.C. for 90% equilibration between the gas in the spirometer and the lungs was calculated and termed the "mixing ventilation". This is a closed-circuit index similar to that described by Becklake and Goldman (1954).

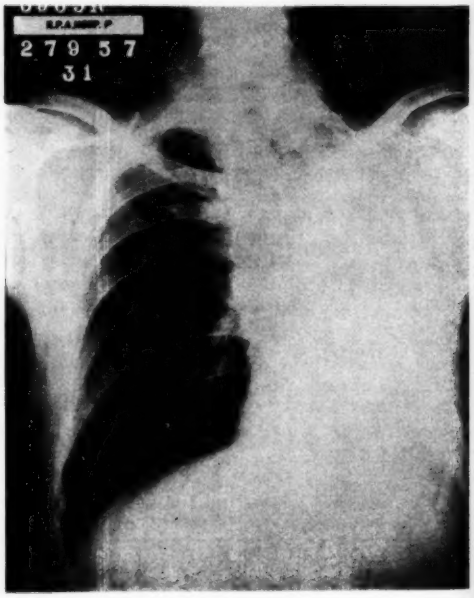

FIGURE II

Postero-anterior chest film of C.F. (Case V), showing the relatively little inflation of the remaining lung

Radiological Estimation of Extent of Collapse

Postero-anterior chest films were used to estimate the extent to which lungs were collapsed in the cases of pneumothorax. The ratio of the area of the collapsed lung on the film to the area of the hemithorax was obtained with a planimeter. This fraction was raised to the power 1·5, and an approximation was obtained of the fraction, by volume, which the lung occupied of its hemithorax.

RESULTS

The results are shown in Tables III and IV and in Figures III to VI. The normal regression lines shown were obtained by Holland and Blacket (1958).

After Pneumonectomy

The normal mean resting value for D_LCO in this laboratory is 22 ml. per minute per millimetre of mercury in young subjects (Holland and Blacket, 1958). In older normal subjects, the value is generally below 20 ml. per minute per millimetre of mercury. Thus D_LCO after pneumonectomy was initially at the lower level of normal in three subjects (though in Case II, that of B.M., it was found to be abnormally low two and a half years later). In the one patient in whom it was measured before and after resection, it fell by more than half. With exercise, D_LCO approached the normal more closely.

B.M. showed little change to account for his clinical deterioration. Although his D_LCO fell, it did not become low enough to be an embarrassment except on moderate exercise. On both occasions he showed carbon dioxide retention, having not only a high arterial tension, but also a high content—23·3 millimoles per litre on the first occasion. His mixing was near to normal on both occasions.

The "mixing ventilation" was variable in the other cases, being raised in Cases I and V and normal in Cases III and IV. In Cases I and V mixing was rapid, but the F.R.C. was low. Thus, the "mixing ventilation" was raised, indicating some non-uniformity of ventilation.

In all post-pneumonectomy cases the total ventilation was greater than normal. However, the increase was much less evident in the alveolar ventilation, except in Case IV (that of R.H., who was very nervous) and Case V.

All patients after pneumonectomy had a resting dead space-tidal volume ratio (corrected for the mouthpiece) greater than 0·3, except R.H. (Case IV), whose tidal volume was greatly increased. The absolute value of the dead space was higher than in the young normal males described by Holland and Blacket (1958). The mean value for the physiological dead space

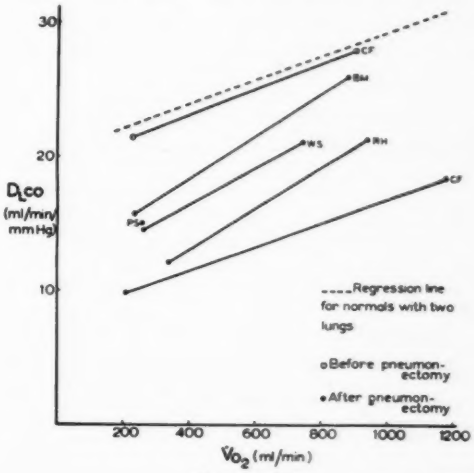

FIGURE III

Showing the diffusing capacity of the pneumonectomy patients at rest, and its increase with exercise

(uncorrected for mouthpiece) after pneumonectomy was 270 ml.; S.D. ±27 ml. In the normal males it was 196 ml.; S.D. ±26 ml. The difference is significant by the *t* test ($P<0·001$).

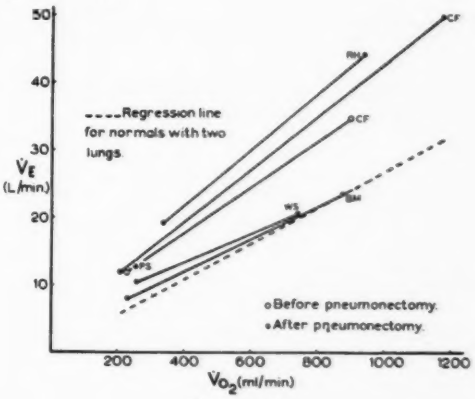

FIGURE IV

Showing the ventilation of the pneumonectomy patients at rest and its increase with exercise

Pneumothorax

The total lung capacity and the vital capacity were reduced on the average by a third when pneumothorax was present. The ratio of residual air to total lung capacity showed no

change in Case VIII (G.C.) and Case IX (A.W.), and was increased in Case VII (R.B.) when the lung was collapsed. The resting ventilation and alveolar ventilation were not altered by the pneumothorax, and in Case IX exercise, with and without the pneumothorax, led to a comparable ventilatory response. Similarly, the dead space and the ratio of dead space to tidal volume showed no consistent change. The diffusing capacity was reduced by the pneumothorax, and for the three patients averaged less than 58% of the control value.

TABLE III

Lung Volumes and Maximum Breathing Capacity Expressed in Absolute Values and as a Percentage of the Value Predicted for a Normal Individual (Two Lungs) by the Formulæ of Needham et alii (1954)[1]

Case Number : Patient	T.L.C.		V.C.		I.C.	E.R.V.	F.R.C.		R.V.		R.V./T.L.C.		M.B.C.	
	Litres	Percentage of Value Predicted	Litres	Percentage of Value Predicted	Litres	Litres	Litres	Percentage of Value Predicted	Litres	Percentage of Value Predicted	Percentage	Percentage of Value Predicted	Litres per Minute	Percentage of Value Predicted
Pneumonectomy :														
I : P.S. ..	2·90	46	2·06	55	1·44	0·66	1·48	39	0·82	32	28·3	69	58	55
II : B.M.—(*a*)[2]	4·67	78	2·66	78	1·71	0·89	2·93	83	2·04	80	43·6	102	—	—
(*b*)	4·57	75	2·41	74	1·39	1·02	3·21	83	2·15	76	47·0	101	27	30
III : W.S. ..	4·58	75	2·15	59	1·69	0·46	2·87	80	2·42	97	52·4	128	62	59
IV : R.H. ..	4·90	73	2·96	78	1·80	1·27	3·07	76	1·80	63	36·7	83	86	83
V : C.F.—(*a*)[3]	5·22	92	3·73	112	2·64	1·15	2·47	73	1·33	57	25·4	62	120	120
(*b*)	3·19	57	2·42	74	1·77	0·67	1·42	44	0·75	33	23·5	58	86	86
Pleural effusion :														
VI : L.M. ..	2·53	39	1·54	43	1·09	0·50	1·45	36	0·95	33	37·5	83	61	62
Pneumothorax :														
VII : R.B.—(*a*)[3]	3·89	59	2·48	52	2·12	0·36	1·79	41	1·43	76	36·8	130	—	—
(*b*)	6·25	94	5·09	107	3·73	1·36	2·52	58	1·16	61	18·6	66	—	—
VIII : G.C.—(*a*)[3]	2·42	43	1·49	48	1·30	0·34	1·11	36	0·77	30	31·7	71	—	—
(*b*)	4·90	86	3·10	100	1·88	1·46	3·02	86	1·56	61	31·9	72	81	89
IX : A.W.—(*a*)[3]	4·81	70	3·30	84	2·59	0·87	2·22	50	1·35	46	28·1	63	96	94
(*b*)	7·20	105	5·05	128	3·20	1·85	4·03	90	2·18	74	30·3	68	134	131

[1] T.L.C., total lung capacity; V.C., vital capacity; I.C., inspiratory capacity; E.R.V., expiratory reserve volume; F.R.C., functional residual capacity; R.V., reserve volume; M.B.C., maximum breathing capacity.
[2] B.M. was studied (*a*) 5 years and (*b*) 7½ years after resection; C.F. was studied (*a*) before and (*b*) 15 months after resection.
[3] In Cases VII, VIII and IX, (*a*) is before and (*b*) after reinflation of the lung.

TABLE IV

Results of Tests of Ventilatory Volume, Blood Gas Concentrations and Diffusion at Rest and during Exercise[1]

Case Number : Patient	Rest or Exercise	Oxygen Uptake (Ml. per Min.)	Ventilation (Litres per Min.)	Physiological Dead Space[1] (Litres per per Min.)	Dead Space[1] Tidal Volume Ratio	Alveolar Ventilation (Litres per Min. per Square Metre)	Arterial Blood			D_LCO (Ml. per Min. per Mm. Hg)
							pH	Carbon Dioxide Tension (Mm. Hg)	Oxygen Saturation (Percentage)	
Pneumonectomy :										
I : P.S.—(*a*)	Rest	255	12·7	205	0·37	3·8	7·52	31·5	93·3	15·0
II : B.M.—(*a*)[2]	Rest	230	7·9	222	0·44	2·1	7·39	45·7	95·5	15·7
	Exercise	877	23·5	299	0·31	8·4	7·35	45·6		25·9
(*b*)	Rest	228	7·6	204	0·51	2·2	7·40	49·9	96·3	8·6
III : W.S. ..	Rest	257	10·4	210	0·42	3·0	7·44	35·7	96·0	14·6
	Exercise	741	20·5	298	0·29	7·8	7·37	41·3	94·7	21·2
IV : R.H. ..	Rest	337	19·2	208	0·23	7·1	7·57	20·3	95·9	12·2
	Exercise	936	44·1	290	0·35	13·6	7·45	26·0	95·9	21·3
V : C.F.—(*a*)[3]	Rest	229	11·8	152	0·39	3·5	7·46	34·0	98·2	21·4
	Exercise	899	34·6	317	0·27	14·8	7·36	34·2	98·0	27·9
(*b*)	Rest	208	11·8	163	0·38	3·8	7·47	30·3	95·8	9·8
	Exercise	1174	49·9	288	0·22	23·5	7·33	30·7	98·3	18·4
Pleural effusion :										
VI : L.M. ..	Rest	248	8·0	104	0·32	2·5	7·46	39·7	94·2	7·0
Pneumothorax :										
VII : R.B.—(*a*)	Rest	312	11·9	228	0·34	3·6	7·42	35·4	96·2	10·2
(*b*)	Rest	318	11·1	170	0·25	3·7	7·42	36·0		21·8
VIII : G.C.—(*a*)	Rest	245	9·8	173	0·38	3·3	7·47	31·6	88·8	5·7
(*b*)	Rest	214	8·2	162	0·40	2·6	7·44	36·9	96·5	8·6
IX : A.W.—(*a*)	Rest	230	9·3	278	0·41	3·1	7·45	35·0	90·9	7·5
	Exercise	627	24·1	501	0·34	9·4	7·41	35·7	92·8	11·1
(*b*)	Rest	189	9·8	290	0·46	3·0	7·48	36·5	94·1	9·7
	Exercise	796	26·8	515	0·34	12·3	7·37	40·0	95·3	16·8

[1] Dead space and tidal volume corrected to allow for volume of mouthpiece.
[2] B.M. was studied (*a*) 5 years and (*b*) 7½ years after resection; C.F. was studied (*a*) before and (*b*) 15 months after resection.
[3] In Cases VII, VIII and IX, (*a*) is before and (*b*) after reinflation of the lung.

Pleural Effusion

The disturbance of function in the case of pleural effusion was very severe. All volumes and the diffusing capacity were grossly reduced.

DISCUSSION

The general tendency for the function of the lung remaining after pneumonectomy to be better than half the value one would expect for two lungs is clear. Such " compensation " is less apparent in the cases of pneumothorax. The results may now be considered in detail.

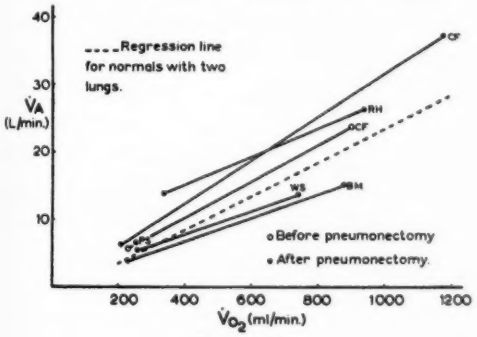

FIGURE V

Showing the alveolar ventilation of the pneumonectomy patients at rest, and its increase with exercise

Lung Volumes and M.B.C. after Pneumonectomy

The inflation of the remaining lung, so that its volume and subdivisions are greater than before, is well known (Cournand and Berry, 1942; Cournand *et alii*, 1950; Friend, 1954; McIlroy and Bates, 1956). The present results show lung volumes greater than half the predicted values in all cases except Case I. However, the relative increase in residual volume and functional residual capacity was less than has usually been found. In only one case (Case III) was the R.V.-T.L.C. ratio significantly greater than the predicted value, and in three cases it was noticeably less. Similarly, by comparing the F.R.C. and T.L.C. (both expressed as a percentage of the predicted value), it is seen that in no case had the F.R.C. of the remaining lung increased significantly more than had the total capacity, and in two cases the F.R.C. had increased relatively less. C.F. (Case V), studied before and after resection, showed no apparent change in the proportion of air in his lungs after normal or forced expiration. However, he showed very little distension either physiologically or radiologically (Figure II). Thus, while increase in volume of the remaining lung usually occurs, its degree is variable, and it does not appear to affect the residual volume particularly.

The small change in the lung volumes of B.M. (Case II) in the 28 months between estimations is not significant, and does not appear to have contributed to his increased disability. This was probably related to his very low M.B.C. At the time of measurement he had lost much of his disability, and on auscultation there was much less wheezing, so it is likely that his severe dyspnœa was caused by airway obstruction.

Dead Space after Pneumonectomy

The finding of a physiological dead space higher than normal after pneumonectomy contrasts with the findings of Fowler and Blakemore (1951), who found, on the whole, a fall in dead space (determined by the nitrogen meter) after resection. The removal of one lung would tend to cause a decrease in the volume of conducting passages by removal of the bronchi

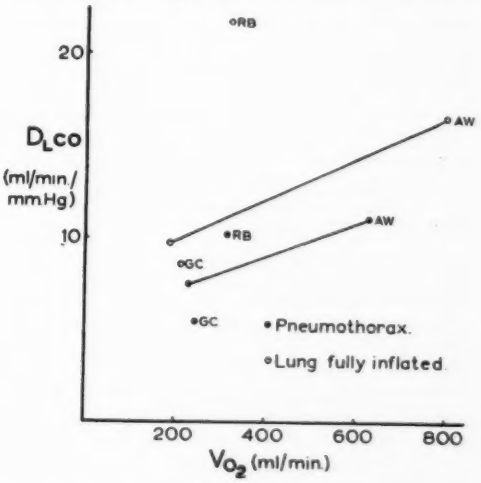

FIGURE VI

Diffusing capacity before and after reinflation, in cases of pneumothorax

on that side. On the other hand, there may also be concomitant dilatation of the remaining passages. However, in view of the decrease found by Fowler and Blakemore, it is likely that in the cases reported here the increase in physiological dead space was due to the presence of regions in which ventilation was in excess of perfusion. An increase of the dead space-tidal volume ratio above 0·3 was found also by Cournand *et alii* (1950). While this indicates an increased dead space, such an increase is not necessarily due to the pneumonectomy, as

an increase in this ratio occurs with age (Joos *et alii*, 1957).

The increase in dead space after pneumonectomy found by Birath *et alii* (1947) may have been due to a genuine increase in the volume of the conducting airways, or it may have been due to a mixing defect. They calculated dead space by the method of Birath (1944), which gives high values for V_D in the presence of inequalities of ventilation. This increase is to be distinguished from the increase in physiological dead space due to inequalities of the ventilation-perfusion ratio; the method of Birath depends on ventilation only.

Diffusing Capacity, Ventilation and Arterial Oxygen Unsaturation after Pneumonectomy

The steady-state carbon-monoxide diffusing capacity showed relatively little change from normal. Apart from the three cases in which it was at the lower level of normality, in one (Case IV) it was a little below normal, and in the other (Case V) its fall was to a little less than half the pre-operative figure. These results are in agreement with those of Cournand *et alii* (1950), who found diffusing capacities within the normal range using the two-level oxygen method of Lilienthal *et alii* (1946). McIlroy and Bates (1956) found values for steady-state carbon-monoxide diffusing capacity which were, on the whole, considerably lower than ours. They used the method of Bates *et alii* (1955), in which end-tidal carbon monoxide concentration is taken as alveolar concentration. However, if there are well-ventilated regions with relatively poor perfusion in the lung, the end-tidal sample will include air with a relatively high carbon monoxide concentration. Thus their method would give a falsely high value for "physiological alveolar carbon monoxide concentration" and a falsely low figure for diffusing capacity. In the method of Filley *et alii*, alveolar carbon monoxide concentration is calculated by means of the arterial carbon dioxide tension, the physiological dead space and the Bohr equation. Regions with a high ventilation-perfusion ratio in this method are regarded as contributing to the physiological dead space, and the high carbon monoxide content in them does not give a falsely high value for alveolar carbon monoxide tension. It is likely that this is the cause for the difference in results obtained by the two methods, especially in view of our finding of a raised physiological dead space in our subjects.

The fall in diffusing capacity with pneumonectomy is, no doubt, due to a decrease in the effective alveolo-capillary surface area and/or the pulmonary capillary blood volume (see appendix for detailed relations). After a pneumonectomy, the resting cardiac output is normal (Cournand *et alii*, 1950), and the resting pulmonary artery pressure is not raised (Cournand *et alii*, 1950). Thus it would appear that there are more vessels patent at rest in the remaining lung than before resection. In this case, neither the alveolo-capillary surface area nor the pulmonary capillary blood volume would be reduced to half the pre-operative value. While a reduction would occur, it would not be so great as 50%, and the diffusing capacity could stay near the normal range.

With exercise, the diffusing capacity approached the normal values more closely in most cases. The rise is attributed largely to the opening up of even more capillaries, with increase in the membrane surface area and pulmonary capillary blood volume.

The arterial oxygen saturation was a little reduced in Case I and at the lower limit of normal in several other cases, but in no case was the diffusing capacity low enough to suggest that a diffusional defect was responsible; increased venous admixture was probably the cause.

In Case V (C.F.) the arterial oxygen saturation was high both at rest and with exercise before pneumonectomy, but after resection it was somewhat reduced, rising with exercise. This rise of oxygen saturation on exercise is not seen when the decrease in saturation is due to a diffusion defect, but is seen when there is a disturbance of ventilation-perfusion ratios (Motley, 1958). The rise is frequently seen in older persons (Joos *et alii*, 1957), and is caused by improvement of the ventilation of some regions as the subject exercises. The fall in diffusing capacity in Case II (B.M.) between the studies did not cause any fall in oxygen saturation; at the time of the second study, his saturation was over 95% when he was exercising at an oxygen consumption of over 650 ml. per minute (the full results are not shown, as a leak in the Douglas bag precluded exact measurement).

The results do not support the suggestion of McIlroy and Bates (1956) that the lowering of diffusing capacity after pneumonectomy necessitates an increased ventilation. Figures IV and V show that in some cases in which total ventilation is raised, alveolar ventilation is normal, and thus that the increase in ventilation was due to the raised physiological dead space. The high alveolar ventilation of R.H. (Case IV) was undoubtedly due to nervousness. C.F. (Case V) had the lowest diffusing capacity

and a high alveolar ventilation, but the possibility of any cause-and-effect relationship is ruled out by the improvement in his arterial oxygen saturation after exercise. The method used for determination of diffusing capacity by McIlroy and Bates would tend to produce a false relationship between D_LCO reduction and excessive ventilation, since the patients with ventilated but unperfused regions, and thus with increased ventilation, would have a falsely low D_LCO.

Pneumothorax

The decrease in lung function in pneumothorax is apparent. In general, the lung volume change closely paralleled the change estimated radiologically (Tables III and V). The diffusing capacity was not so reduced as were the lung volumes in Cases V and IX, and its reduction had no consistent relationship to the lung-volume reduction. However, it was always reduced in pneumothorax. This agrees with the observations of Kjerulf-Jensen and Kruhøffer (1954), who, using the rebreathing method of Kruhøffer (1954), found increase of diffusing capacity as the lung reexpanded. The slight arterial oxygen unsaturation found in Cases VIII and IX was probably not due to lowered diffusing capacity, but rather to venous admixture.

TABLE V

The Ratios of Lung Volumes (Estimated by Two Different Methods) and of Diffusing Capacity, before Reinflation (a), *to Those after Reinflation* (b), *in Cases of Pneumothorax*

Case Number, Patient	Lung Volume (*a*) / Lung Volume (*b*) (Radiological)	T.L.C. (*a*) / T.L.C. (*b*)	D_LCO (*a*) / D_LCO (*b*)
VII: R.B. ..	0·64	0·62	0·47
VIII: G.C. ..	0·55	0·49	0·66
IX: A.W. ..	0·66	0·67	0·76

The low D_LCO after reinflation in Cases VIII and IX may have been due to failure of capillaries to open up after reexpansion, but was probably due to lung disease. The clinical diagnosis of emphysema had been made in Case VIII, and a bulla in the uncollapsed lung was seen in Case IX. We have observed several patients with similar findings—a lowered D_LCO, but normal M.B.C. and R.V.-T.L.C. ratio. In the absence of definite evidence regarding the causation, we have ascribed this pattern to aging.

Not enough measurements have been made to state whether the diffusing capacity in cases of pneumothorax is higher than one would have predicted from the lung-volume reduction; but our impression is that it is, since at the time of study of Case VII our analytical methods were less accurate. One would expect D_LCO to be relatively higher for the same reason as pertains after pneumonectomy.

The ability of the remaining lung to take over part of the resected lung's functions is a feature of pneumonectomy. It also occurs in chronic pneumothorax. As no measurements have been made during the first few hours of acute pneumothorax, the explanation of the respiratory distress is not clear.

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APPENDIX

The relationship between the apparent diffusing capacity of the lung as a whole (D_L), which is what is determined in the routine measurement of diffusing capacity, the diffusing capacity of the pulmonary membrane (D_M), the rate of reaction of hæmoglobin with intracellular hæmoglobin, and the pulmonary capillary blood volume has been derived by Roughton and Forster (1957). It is:

$$\frac{1}{D_L}=\frac{1}{D_M}+\frac{1}{\theta Vc}$$

where D_L is the apparent diffusing capacity of the lung as a whole, in millilitres per minute per millimetre of mercury, and diffusion of the gas is considered as proceeding from the gaseous state in the alveolus to the state in combination with hæmoglobin in the red corpuscle; D_M is the diffusing capacity of the effective alveolo-capillary membrane in millilitres per minute per millimetre of mercury; θ is the number of millilitres of gas (say carbon monoxide) taken up by the red cells in 1 ml. of blood per minute per millimetre of mercury gradient of partial pressure of dissolved gas between the plasma and the interior of the red cell; and Vc is the pulmonary capillary blood volume (millilitres). $\frac{1}{D_L}$ is the total resistance to diffusion; $\frac{1}{D_M}$ is the membrane resistance to diffusion; and $\frac{1}{\theta Vc}$ is the intracapillary resistance to diffusion. These resistances are analogous to electrical resistances where $\frac{1}{D_M}$ and $\frac{1}{\theta Vc}$ are in series.

From the foregoing, it can be seen that D_L would be lowered by a decrease in D_M, which, in turn, could be due to a decrease in the effective alveolo-capillary membrane area, or to an increase in its mean thickness. D_L would also be lowered by a decreased affinity of hæmoglobin for the gas in question, or by a decrease in the pulmonary capillary blood volume. In practice, several factors frequently operate together.

ACUTE NECROTIZING GLOMERULITIS

THE CLINICAL FEATURES AND PATHOLOGY IN NINE CASES[1]

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SUMMARY

Nine cases of necrotizing glomerulitis have been studied. The lesion was found in association with pulmonary hæmorrhage, or in middle-aged males with anuria. There were characteristically a low incidence of hypertension and œdema, an insidious onset, a rapid course and a uniformly fatal outcome, usually in uræmia. No causal factors were discovered. The renal lesion consists of necrosis and disintegration of the structure of the glomerular tuft. Cellular proliferation is variable in amount and disorderly. The glomeruli may be replaced by collections of inflammatory and spindle cells or of fibrous tissue. The tubules are spared. The interstitial tissue is œdematous, and may be infiltrated by inflammatory cells. Rarely, renal arteries or arterioles show fibrinoid change without any surrounding inflammatory reaction. Except for pulmonary hæmorrhage in some cases, there are no lesions in other organs. It is concluded that the process shows affinities to both proliferative glomerulonephritis and polyarteritis nodosa, but its exact nature remains to be determined.

IN the course of his Croonian lectures on "The Natural History of Bright's Disease", Ellis (1942) made the following statement:

> In more severe cases, particularly those dying with suppression after one or two weeks, acute fibrinoid necrosis of the arterioles and of the glomerular tufts is characteristic, and early epithelial crescent formation may be seen. When death occurs after the rapidly progressive course, the outstanding feature is the formation of large epithelial crescents with associated hæmorrhage into Bowman's space; acute fibrinoid necrosis of the arterioles is common, and a few cases show an intense inflammatory infiltration of the interstitial tissue with "explosive" lesions of the glomeruli and definite periglomerular inflammatory reaction.

Inherent in this statement is the assumption that these severe glomerular lesions result from an intensification of the pathological processes responsible for proliferative glomerulonephritis. This view has been questioned by Davson, Ball and Platt (1948) in the course of a study of the renal lesions of polyarteritis nodosa, and by Wainwright and Davson (1950). In both these papers cases were presented in which necrotizing glomerulitis was associated with the vascular lesions of polyarteritis nodosa. The second paper described, in addition, two cases of severe necrotizing glomerulitis without arterial lesions. Such cases appear to be extremely rare. One was included among those studied by Gray (1933), but there was no comparable example in the series of Russell (1929) or of Bell (1937). More recently, necrotizing glomerulitis has been found in association with pulmonary capillary hæmorrhage (Parkin *et alii*, 1955) and has been described in patients with prolonged anuria (Dick, 1957; Alwall *et alii*, 1958). In the cases reported in two papers entitled "Acute Necrotising Glomerulonephritis" (Dunn and Montgomery, 1941; Blainey, 1952), the patients appear to have suffered from cortical necrosis, tubular necrosis or proliferative glomerulonephritis, and not from the particular lesion with which we are concerned. We have now encountered nine patients (Table I) whose main lesion was necrosis of glomeruli. Clinically, this led to oliguria or anuria, and to death in uræmia.

CLINICAL FEATURES

In four cases the glomerular lesion was associated with pulmonary hæmorrhage. The course of the lesion in three cases has previously been described (Stanton and Tange, 1958). The fourth patient was a man, aged 39 years, who had suffered from recurrent hæmoptysis for seven months, for which no cause could be demonstrated; he showed no urinary abnormalities until he developed hæmaturia seven weeks before he died in uræmia; signs of renal involvement appeared 10 days, two weeks, seven weeks and seven months after onset of the lung lesion. All patients suffered from terminal

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oliguria or anuria, and two from hæmaturia; none was hypertensive, and none showed œdema. In only one case was the antistreptolysin titre estimated, and it was within normal limits.

The second group comprised five males, whose ages fell between 50 and 65 years; the duration of their illness was between one and four weeks. The onset in three cases was heralded by vomiting and oliguria, progressing to anuria; one of these patients also showed hæmaturia. In the fourth case the illness commenced with painless hæmaturia, and anuria supervened after three weeks. The fifth patient was admitted to hospital with a respiratory infection, and died the next day. He passed no urine while he was in hospital. Of three patients with œdema, two were hypertensive; but both had been treated for cardiac failure, and there were indications that both the œdema and the hypertension had been present in some degree before their final illness. All patients were

TABLE I

The Clinical Features Associated with Acute Necrotizing Glomerulitis

Patient, Sex and Age (Years)	Duration of Illness	Presentation	Other Manifestations	Termination	Investigations	Other Features
J.S., M., 21	11 days	Tightness in the chest, hæmoptysis	Tiredness, dyspnœa, epididymitis. B.P. 160/80 mm. Hg, crepitations, albuminuria "1/8"	Hæmoptysis, dyspnœa, shock, oliguria, ? anuria	Hæmoglobin value, 6·3 grammes per 100 ml. Leucocytes 10,000 per c.mm. (neutrophils 80%) Chest X-ray film: coarse mottling of lung fields	Unexplained hæmoptysis one year previously
I.W., M., 45	3 weeks	Sore throat, fever, cough	Hæmoptysis; hæmaturia 2 weeks after onset; B.P. 150/90 mm. Hg, crepitations	Hæmoptysis, dyspnœa; shock; anuria for 3 days	Hæmoglobin value, 6·8 grammes per 100 ml. Leucocytes, 20,000 per c.mm. (neutrophils 93%); blood urea content, 60 mg. per 100 ml., 140 mg. per 100 ml. Chest X-ray film: mottling of lung fields	
M.S., F., 22	8 weeks	Malaise, weakness, dyspnœa, hæmoptysis	B.P. 110/70 mm. Hg, crepitations, albuminuria (a trace)	Upper abdominal colic, vomiting and anuria 7 weeks after onset	Hæmoglobin value, 4·4 grammes per 100 ml. Leucocytes, 9000 per c.mm. (neutrophils 77%), blood urea content 230; 300 mg. per 100 ml. (terminal) Chest X-ray film: diffuse mottling, middle and lower lobes	Dyspepsia; blood mixed with food on self-induced vomiting
X.Z., M., 39	9 months	Repeated hæmoptysis	B.P. 120/80 mm. Hg, breathlessness after a blood transfusion; urine normal to ward tests and on microscopic examination	Hæmaturia, vomiting 7 months and oliguria and uræmia 8 months after onset	Hæmoglobin value, 5·0 grammes per 100 ml. Leucocytes, 8000 per c.mm.; blood urea content 216 mg. per 100 ml. Antistreptolysin titre, 50 units	
G.H., M., 65	4 weeks	Painless hæmaturia	B.P. 140/70 mm. Hg; no œdema	Anuria one week, convulsions	Blood urea content, 146 mg. per 100 ml.	
C.H., M., 64	4 weeks	Malaise, sweating, rigors, vomiting	B.P. 190/120 mm. Hg; systolic murmur, crepitations, œdema	Anuria one week after onset, fever; terminal jaundice	Hæmoglobin value, 10·9 grammes per 100 ml. Leucocytes, 8000 per c.mm.; blood urea content 130; 250 mg. per 100 ml. Laparotomy: blood-stained fluid in peritoneum	Swelling of ankles for 3 months; mercurial diuretics prescribed
P.E., M., 61	2 weeks	Headache, vomiting	Hæmaturia 3 days after onset, oliguria, shivers, sweating; B.P. 165/70 mm. Hg; crepitations, ankle œdema, spider nævi	Jaundice, anuria, melæna	Leucocytes, 15,000 per c.mm. (neutrophils 90%); blood urea content 320 mg. per 100 ml. (terminal)	Liver showed lobular hyperplasia
A.J., M., 59	1 week	Vomiting, twitching, hiccups	B.P. 210/120 mm. Hg	Anuria, pulmonary œdema	Blood urea content 280 mg. per 100 ml.	Dyspnœa on effort for 2 years; nocturnal dyspnœa for 8 months
E.B., M., 50	2 weeks	Cough, chest pain, dyspnœa	B.P. 95/60 mm. Hg; crepitations and rhonchi; pericardial and pleural friction rubs	Anuria, died within 24 hours of admission to hospital		Chronic bronchitis and emphysema

anuric and their blood urea levels were elevated before they died. One patient had an intermittent fever, and the remainder were afebrile. Such investigations as were performed shed no light upon the ætiology of the condition.

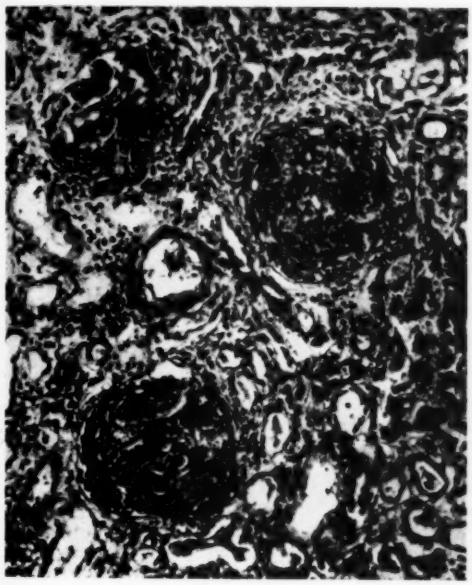

FIGURE I

Photomicrograph of the kidney, showing three glomeruli replaced by amorphous eosinophilic material containing pyknotic nuclei. There are inflammatory cells in the damaged tufts and in the interstitial tissue. The vessel between the three glomeruli is normal. (Hæmatoxylin and eosin stain, ×135)

Pathological Appearances

The kidneys are relatively normal in size, though sometimes swollen by œdema and flecked by points of hæmorrhage throughout the cortex. In one case the kidneys are smaller and finely granular, and on microscopic examination the renal arteries and arterioles show intimal thickening.

On microscopic examination (Table II) the glomeruli are most affected, severe and extensive lesions being present in all cases. Except in one case in which a few are spared, all glomeruli examined are damaged, though not to the same degree. The striking feature is the replacement of the whole or the greater portion of the tuft by deeply eosinophilic, amorphous material, containing a small number of pyknotic nuclei, and arranged in contiguous or confluent masses (Figure I). In some glomeruli the necrotic material is not aggregated, but dispersed among surviving endothelial cells or fibroblasts (Figure II). All such glomeruli are considerably swollen (Figure III). Nearly always the structure of the glomerulus is destroyed, but in some cases normally arranged capillaries remain in a segment of the tuft (Figure IV); less often the damage is restricted to a small segment of the tuft (Figure V), and an occasional glomerulus appears on a first inspection to have escaped injury, but amorphous eosinophilic material may be seen in the interstices between the capillaries. This may represent either the earliest or the mildest manifestation of the lesion.

At the edges of the necrotic material may be found blurred nuclear remnants or viable

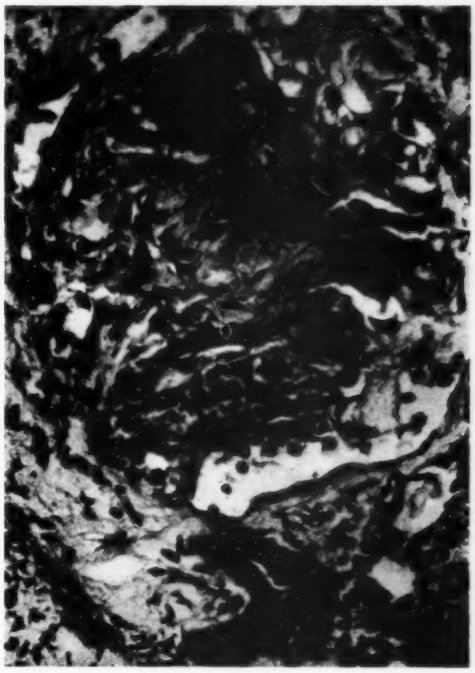

FIGURE II

Photomicrograph of the kidney, showing a glomerulus containing eosinophilic material interspersed with spindle cells which appear to divide the tuft. There are a few capillary loops still present in one segment. The walls of the afferent arteriole show fibrinoid change. (Hæmatoxylin and eosin stain, ×390)

proliferating cells. These are spindle cells, probably fibroblasts, or endothelial cells, irregularly arranged and with very little cytoplasm. Characteristically, they are disposed in the following four ways: (i) Spindle cells

TABLE II

Microscopic Appearances of the Kidney in Acute Necrotizing Glomerulitis[1]

Subject	Cortical Pattern	Complete Glomerular Damage	Partial Glomerular Damage	Glomeruli Spared	Glomerular Necrosis	Cellular Proliferation	Giant Cells	Polymorph Infiltration	Hyalinization	Capsular Adhesions	Capsular Basement Membrane	Circumferential Cellular Proliferation	Pericapsular Fibrosis	Pericapsular Inflammatory Cell Infiltration	Periglomerular Tubular Damage	Tubule Basement Membranes	Tubule Cells	Tubule Lumina	Tubule Contents	Interstitial Œdema	Interstitial Inflammatory Cell Infiltration	Interstitial Fibrosis	Afferent Arterioles	Arteries	Other Features
J.S.	N	60%	40%	–	+ + +	+ + +	+	+	–	+	Lost	+	–	+	+	Int.	N	N	R.B.C., P.R.	+	+	–	N	Fibrn.	Arterial damage confined to one vessel
I.W.	N	100%	–	–	+ + +	+ + +	+	+ +	–	+	Lost	+	–	+	+	Int.	N	N	R.B.C., P.R.	+	+ +	–	N	N	In the glomeruli, patches of necrosis interspersed with viable cells. Total disorganization of glomerular architecture
M.S.	N	100%	–	–	+	+	–	+	+ +	+	Lost	+	+	+	–	Int.	N	N	R.B.C., P.R.	–	–	–	N	N	Combination of necrosis and repair suggests two separate attacks
X.Z.[2]	N	60%	40%	–	+ +	+	–	+	–	+	Th.	–	–	–	–	Int.	N	Dil.	P.R.	+	+	+	Fibrn.	N	Surviving capillaries occupy only a tiny segment of tuft. Autopsy specimen (3 weeks later) shows more interstitial fibrosis and cellular proliferation
X.Z.[3]	N	80%	20%	–	+	+ +	–	+	+	+	Th.	–	–	–	–	Int.	N	Dil.	R.B.C., P.R.	+	+	+	Fibrn.	N	
G.H.	N	35%	60%	5%	+ + +	+	–	–	–	+	Lost	+	–	+	+	Int.	N	Dil.	R.B.C., P.R.	+	+	–	N	N	Hæmorrhage into capsular spaces and tubular lumina prominent feature
C.H.	N	100%	–	–	+ + +	+	–	–	–	+	Lost	+	–	+	+		N		Polys. R.B.C.		+		N	N	Severe post-mortem degeneration evident
P.E.	N	90%	10%	–	+ +	+ + +	+ + +	+	+	+ + +	Lost	+ + +	– +	+ + +	+ + +	Int.	N	Dil.	R.B.C.	+ +	+ +	–	N	N	
A.J.	N	95%	5%	–	+	+ + +	+ + +	–	+	+ + +	Lost	+ + +	+	+ + +	+ + +	Int.	N	Dil.	P.R.	+ +	+ +	+	Th.	Th.	
E.B.	N	66%	34%	–	+ +	+ + +	+ + +	+	–	+ + +	Lost	+ + +	–	+ + +	+ + +	Int.	N	N	R.B.C., P.R.	+ +	+ +	–	Fibrn.	Fibrn.	

[1] Abbreviations: Th., thickened; Int., intact; Dil., dilated; R.B.C., red blood corpuscles; Polys., neutrophil leucocytes; P.R., cosinophilic material; Fibrn., fibrinoid change; N, normal.

[2] Biopsy specimen.

[3] Autopsy specimen.

may divide the tuft (Figures II and VI). (ii) Endothelial cells are situated to one side of masses of necrotic material and may simulate crescent formation. (iii) Either type or both types of cell may be interspersed with necrotic

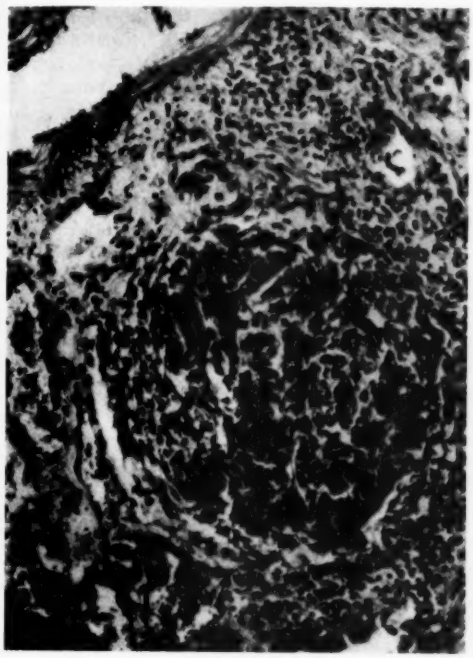

FIGURE III

Photomicrograph of the kidney, showing a glomerulus which is considerably swollen and replaced by structureless eosinophilic material. There are many neutrophil leucocytes in the damaged glomerulus, and many plasma cells among the inflammatory cells infiltrating the interstitial tissue. The walls of the large vessel are normal. (Hæmatoxylin and eosin stain, ×180)

material. (iv) Either type or both types of cell may be arranged circumferentially about necrotic material. Giant cells have formed in some glomeruli (Figures VII and VIII), and there is infiltration by neutrophil leucocytes, though their numbers are usually small and many are necrotic (Figure III).

The tuft is adherent to the capsule except when the damage to the glomerulus is only slight or segmental. Often its basement membrane has ruptured, and a mass of necrotic material, fibres and proliferating cells bulges into the surrounding tissue. Sometimes the swollen tuft or proliferating cells appear to have herniated into a proximal tubule (Figure IX).

The glomerulus may be completely replaced by a meshwork of cells and fibres, which blend with the reticular framework of the surrounding tubules (Figures VII and VIII). Round the tuft are numbers of inflammatory cells (Figure III), and the tubules may have atrophied or disintegrated and their reticulum contracted or become condensed (Figure VII). Elsewhere, the tubule epithelium is normal, and frequently the lumina are dilated and contain red cells or an eosinophilic coagulum, probably protein. The interstitial tissue is œdematous and sparsely infiltrated by, or contains, small collections of inflammatory (including plasma) cells (Figure III). In two cases there is slight interstitial fibrosis. In most cases arteries and afferent arterioles are normal, though necrotic change

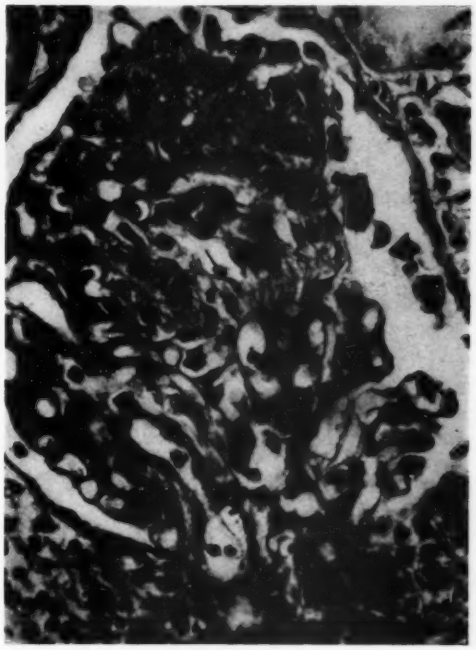

FIGURE IV

Photomicrograph of the kidney, showing a glomerulus with a mass of amorphous eosinophilic material alongside normally arranged capillaries. There is a second deposit of eosinophilic material outside the capsule below the pedicle of the tuft. (Hæmatoxylin and eosin stain, ×390)

seems to spread from the tuft into the immediately adjacent portion of the afferent arteriole (Figure VI); this is especially noticeable if the change is severe. In one case there is widespread eosinophilic swelling of the walls of

arteries and arterioles without any surrounding inflammatory reaction. In other cases this change is present in a few small vessels (Figure II). In two cases a number of glomeruli are hyalinized, and this is thought to represent a later stage of the lesion. Deeply eosinophilic necrotic material is sometimes present in partly hyalinized tufts or in neighbouring glomeruli (Figure X).

FIGURE V

Photomicrograph of the kidney, showing a glomerulus with a small mass of eosinophilic material and similar material within the interstices of the capillary loops. The arterioles of the tuft are normal. (Hæmatoxylin and eosin stain, ×570)

Except for lung lesions in a number of cases (Stanton and Tange, 1958) and epididymitis in one of these, no significant changes were noted in other organs.

DISCUSSION

Apart from the patients who had had antecedent pulmonary hæmorrhage, these glomerular lesions were observed in a group of middle-aged males with anuria. Hypertension and œdema were exceptional, and probably coincidental findings. Unless manifested by hæmaturia, the onset was insidious, and in consequence most patients continued at work in the earlier days of their illness.

In patients with proliferative glomerulonephritis, continuing activity is associated with a poorer prognosis (Ellis, 1942); but in the present series it is impossible to relate these two features. The first is probably due to an insidious onset (common to other lesions producing anuria) and the second to the severity and completeness of the glomerular damage.

The characteristic histological changes are necrosis of glomeruli and disintegration of capillary loops. Proliferation of surviving cells is haphazard and disordered, and appears directed towards the production of granulomatous masses or fibrosis, and not towards restoration of glomerular structure. Although these twin processes produce complete or almost complete interference with blood flow through the glomeruli, there is relatively little damage to the tubules. This may be explained by the

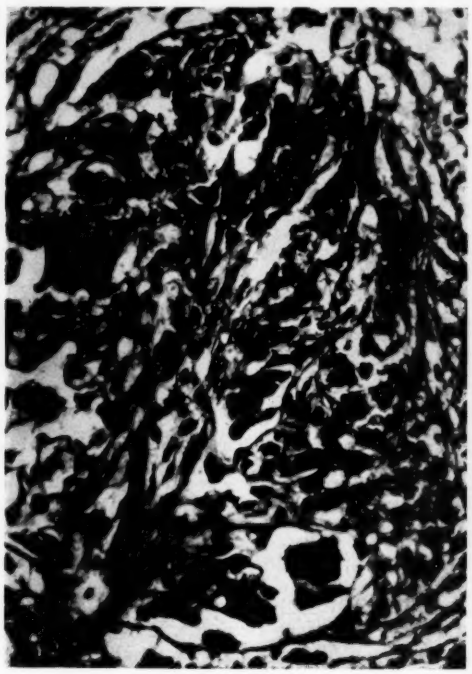

FIGURE VI

Photomicrograph of the kidney, showing a glomerulus in which there is extensive adhesion between tuft and capsule. The tuft is divided by strands of spindle cells and contains small collections of eosinophilic material. Similar material is present in the wall of the afferent arteriole. (Hæmatoxylin and eosin stain, ×390)

demonstration of an extraglomerular arterial supply to the tubules (Bialestock, 1957). It is of considerable significance that this combination of severe glomerular damage and sparing of the tubules is not associated with hypertension. Damage to glomeruli is clearly independent of arterial lesions, though these are present occasionally, and when the glomerular lesions are severe, necrosis extends into the proximal portion of the afferent arteriole.

Since the onset of the illness is not clearly defined, it is impossible to assess accurately the age of the lesions or to determine the sequence in which they appear. A similar difficulty confronted Brun *et alii* (1958), who performed renal biopsies on a number of patients with anuria due to severe glomerulonephritis; they

FIGURE VII

Photomicrograph of the kidney, showing glomeruli replaced by mingled eosinophilic material, spindle cells and fibrils. These blend with the collapsed reticulum resulting from damage to the tubules immediately adjacent to the glomerulus. There is a giant cell in one damaged glomerulus, and below and to the left a collection of round cells and normal vessels. (Hæmatoxylin and eosin stain, ×135)

concluded that collagen formation occurred in damaged glomeruli as early as the fifteenth day. Wachstein and Lange (1958) produced glomerulonephritis in rabbits with duck anti-kidney serum, and in these experiments necrosis succeeded an early exudative and proliferative response eight to 16 days after administration of the serum. Fibrosis could be seen in damaged glomeruli as early as the sixteenth day. These observations suggest that the renal appearances in our cases are consistent with an illness of short duration.

FIGURE VIII

Photomicrograph (at higher magnification) of portion of a glomerulus shown in Figure VII. Round a multinucleate giant cell, spindle cells and fibrils blend with the collapsed tubular reticulin framework. (Hæmatoxylin and eosin stain, ×390)

The nature of the causal agent is obscure, and exactly comparable lesions have not been produced by experimental means, although a number of agents are known to produce selective renal vasospasm. These include staphylococcal toxin, vasopressin, epinephrine and the application of electrical stimuli to parts of the cerebral cortex. However, selective renal vasospasm in the experimental animal results in cortical necrosis (De Navasquez, 1938; Thal, 1955), rather than the selective glomerular necrosis found in these cases. Krakower and Greenspon (1958) have shown that nephrotoxic antigens have an affinity for glomerular capillary basement membrane 10 to 20 times greater than for that of other capillaries. Further studies on nephrotoxic antigens to elucidate their nature might shed light upon the puzzling selective glomerular lesions seen in this group of cases. The focal necroses seen in glomeruli in which

portion of the tuft is intact resemble those found in subacute bacterial endocarditis (Bell, 1932), in malignant hypertension (Wilson and Byrom, 1939), in systemic lupus erythematosus (Muehrcke *et alii*, 1957), in scleroderma (Fisher and Rodnan, 1958) and in Henoch-Schönlein

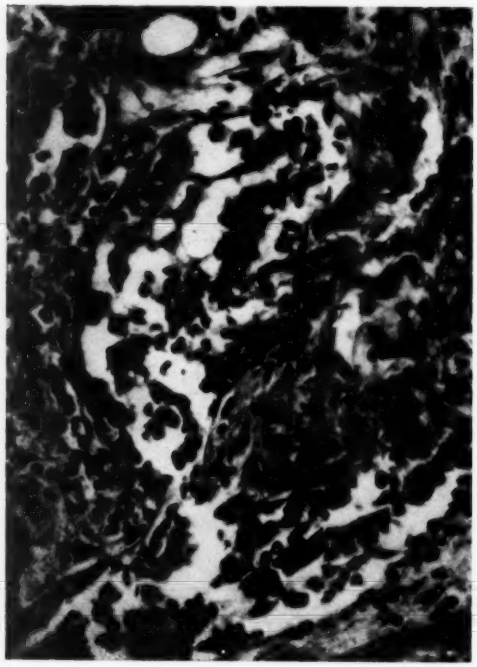

FIGURE IX

Photomicrograph of the kidney, showing a damaged glomerulus with proliferating cells extending into the proximal tubule. (Hæmatoxylin and eosin stain, ×390)

purpura (Vernier *et alii*, 1958); but necrotizing glomerulitis is usually distinguished from these conditions by the severity, extent and frequency of the glomerular lesions.

The microscopic appearances of the glomerular lesions closely resemble those of polyarteritis nodosa (Davson *et alii*, 1948; Wainwright and Davson, 1950) and of Wegener's granulomatosis (Wegener, 1939; Fahey *et alii*, 1954); but arterial lesions are usually absent in necrotizing glomerulitis or, if present, consist of fibrinoid change without any surrounding inflammatory reaction. Moreover, the interstitial infiltration is predominantly round-celled. The predilection of necrotizing glomerulitis for middle-aged males (though cases have been reported in younger patients and in females), together with the infrequent occurrence of hypertension and œdema in this condition, suggests that it is a different process from proliferative glomerulonephritis. However, both necrotic and proliferative lesions are found following unexplained pulmonary hæmorrhage (Stanton and Tange, 1958). When we recall the occasional presence of arterial lesions in these cases, it is apparent that no sharp distinction can be drawn between them and either polyarteritis or proliferative glomerulonephritis. However, such a difference probably exists, and will be established only when we have greater knowledge of all three conditions.

Within our own experience, the incidence of necrotizing glomerulitis has increased sharply over the past decade. Whatever its significance, this increase should offer further opportunities for studying the lesion and determining its cause.

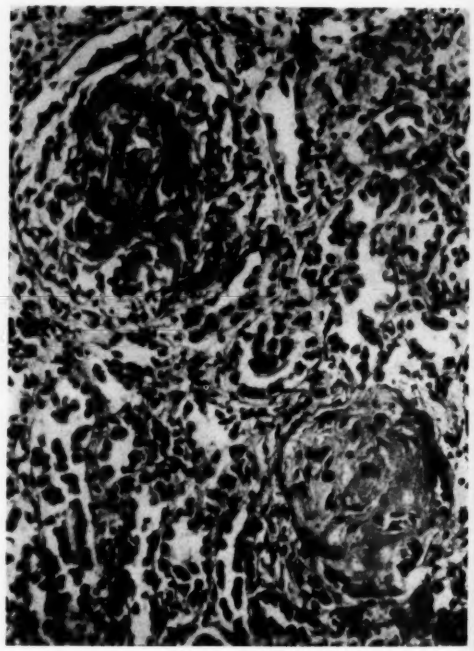

FIGURE X

Photomicrograph of the kidney, showing a glomerulus transformed into fibrous tissue. In an adjacent glomerulus there is deeply eosinophilic structureless material. (Hæmatoxylin and eosin stain, ×225)

ACKNOWLEDGEMENTS

For permission to study these patients, our thanks are due to the members of the honorary medical staffs of the Royal Melbourne Hospital and the Alfred Hospital, and to the Deputy Commissioner of Repatriation.

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HEALED DISSECTING ANEURYSM OF THE AORTA

A REPORT OF THREE CASES[1]

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SUMMARY

Three cases of healed dissecting aneurysm diagnosed during life are presented. Two had several points in common—an onset during mild exertion, external leakage into the pleural cavity and a similar site of intimal tear. The third was characterized by involvement of the aortic valve ring with aortic incompetence, dissection of the great vessels with unequal peripheral pulsations, and occlusion of the left renal artery causing infarction and atrophy of the kidney. In each case there was endothelialization of the false sac, with formation of atheroma-like plaques in one instance. Histologically, the striking features throughout the media were loss of elastic tissue and scattered areas devoid of nuclei.

The so-called healed dissecting aneurysm is a temporary state, and further fatal complications are probable.

DISSECTING ANEURYSM of the aorta is being diagnosed during life with greater frequency, because there is an increasing awareness of the condition and its accompanying clinical picture. Furthermore, it is not an especially rare condition. However, the establishment of a distal point of reentry, allowing free flow of blood in the aorta and the aneurysm—the double-barrelled aorta—is quite uncommon. Peery (1936) found about 80 cases reported in the literature, and there have been others since (Glendy *et alii*, 1937; Weiss *et alii*, 1940; Graybiel and Sprague, 1941; Mote and Carr, 1942; Drury, 1955). Of course, these cases are more likely to be published than those in which rapid death occurs. Three such cases appearing within a few months of each other in the Royal Adelaide Hospital have prompted this report.

CASE I

The patient was a housewife, aged 49 years, who developed a severe pain "like a stab with a knife" in the right side of her chest posteriorly whilst walking. She went to bed, but the pain did not completely leave her, and there was a series of exacerbations of increasing severity. The pain radiated to the right shoulder and later extended to the abdomen. It was aggravated by coughing and deep breathing. She was given opiates, but after four days she developed acute shortness of breath and cough, with blood-stained sputum. She was admitted to the Royal Adelaide Hospital on October 5, 1956.

Examination revealed her to be a well-built middle-aged woman in severe pain. There was no cardiac enlargement, and the heart sounds were clear, regular and normal. The radial and femoral pulses were present; the blood pressure was 140/90 mm. Hg. There were signs of fluid at the base of the right lung posteriorly, extending up to the seventh rib. Paracentesis thoracis yielded 12 ounces of dark, blood-stained fluid. No other abnormality was found.

The pain abated after several days, but the pleural effusion required four weeks to clear, during which time the patient had an intermittent fever (temperature up to 102° F.). Eleven days after her admission to hospital, a faint systolic murmur was detected at the apex of the heart. This murmur became more audible, and 10 days later it could be heard diffusely over the precordium, but most loudly over the pulmonary area. Serum agglutination tests, a Wassermann test and blood culture, together with examination of the sputum, urine and pleural fluid, failed to reveal any significant cause for the effusion and fever.

An X-ray examination of the chest after the paracentesis thoracis showed some residual fluid at the base of the right lung. Increased width of the arch of the aorta together with some unfolding was noticed. Fluoroscopic screening of the chest six weeks after the patient's admission to hospital confirmed the presence of an aneurysm in the arch and the upper part of the descending aorta, and the diagnosis of dissecting aneurysm with external leakage into the right pleural cavity was made. Throughout the patient's six weeks in hospital no inequality of arterial pulsation was detected, and with the clearing of the effusion in the right pleural cavity she was discharged home.

When she was examined again three months later, she was well and active. Abdominal pulsation was observed, and there was a systolic thrill palpable over the heart, with an early diastolic murmur maximal in the third left intercostal space in the mid-clavicular line.

For the next year the patient was symptom-free, but during the ensuing four months she noticed increasing dysphagia, food tending to "stick in her throat". Twenty-one months after the initial acute attack she was readmitted to hospital, acutely dyspnœic, with a 14 hours' history of severe pain in the chest which had come on while she was asleep in

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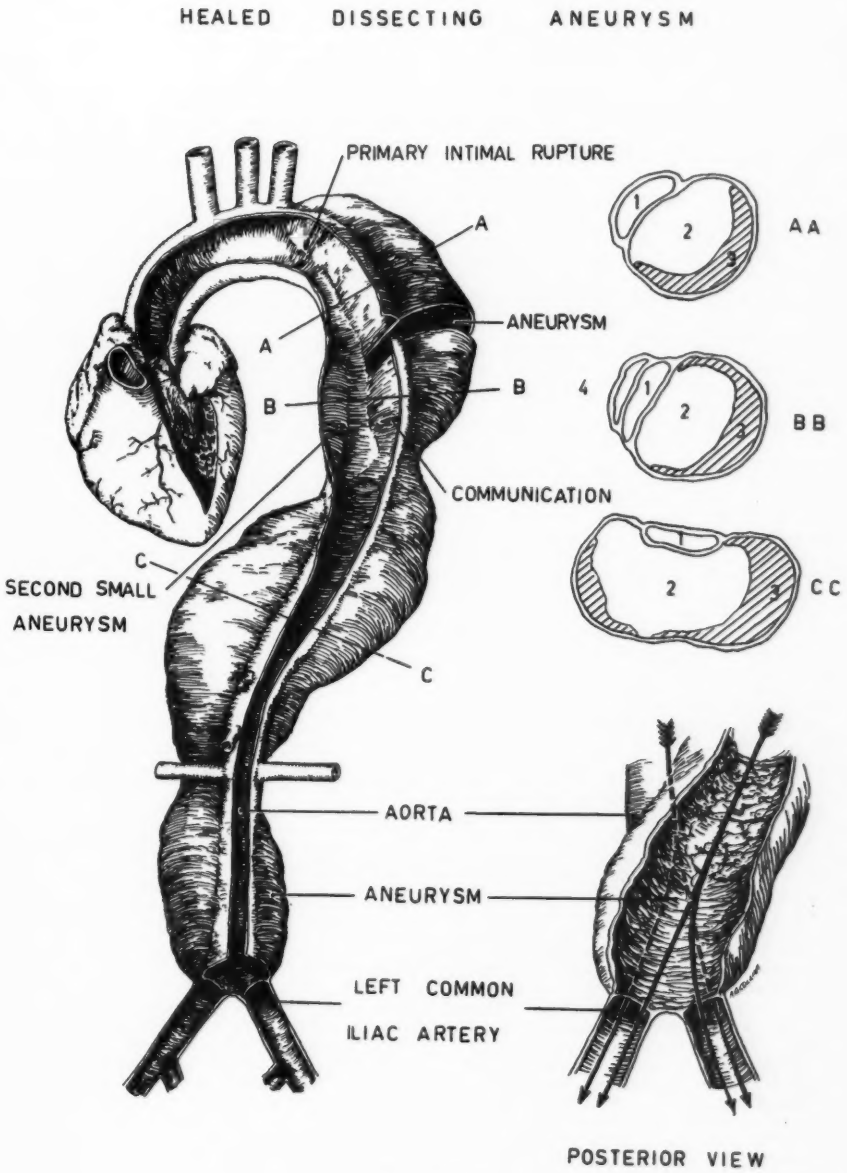

FIGURE I

Healed dissecting aneurysm in Case I, with cross section at planes AA, BB and CC; 1, aortic lumen; 2, dissecting aneurysm; 3, thrombus; 4, second smaller aneurysm

bed. Radial and femoral pulsations were present and equal. There was tenderness over the anterior part of the chest, and a blowing systolic and rumbling diastolic murmur were clearly audible over the left parasternal area. She had severe retrosternal pain and intermittent lumbar pain. Twenty-four hours after her admission to hospital she developed peripheral circulatory failure and died.

Autopsy

At autopsy, the significant findings were confined to the aorta, where there was a large dissecting aneurysm, which had terminated by reentering the aorta at its bifurcation, forming a double-barrelled aorta. There was no adventitial hæmatoma to indicate a terminal external rupture. Occlusion of intercostal and lumbar vessels which arose from the aneurysmal sac may have accounted for her pain; but no satisfactory cause of death was found, apart from cardiac failure. The following description applies to the preserved specimen.

The left ventricle was moderately enlarged and hypertrophied, and the ascending and transverse portions of the aortic arch were normal. The descending part of the arch and the remainder of the aorta were obscured by a large dissecting aneurysm, which accompanied the aorta throughout its length and partly enveloped it (Figure I).

Externally, the aneurysm commenced as a saccular dilatation 4·5 cm. in diameter, the most proximal part reaching, but not involving, the left subclavian artery. There was a constriction at a point 5 cm. distal to the origin, where the diameter was reduced to 2·5 cm., and from here the sac dilated again as it passed from the postero-lateral aspect of the aorta to lie immediately posteriorly until the level of the renal vessels was reached. Here there was another constriction, though less marked, and the aneurysm spiralled around the aorta, still further to encroach on the right postero-lateral aspect for the remainder of its course. The sac terminated by tapering down to become confluent with the walls of the aorta at its point of bifurcation.

Throughout its extent, the aneurysm surrounded approximately two-thirds of the original aortic wall, leaving only a thin ribbon of the latter along the anterior surface. The renal, superior and inferior mesenteric arteries arose from this remnant of undissected aortic wall.

The primary intimal tear was transverse in direction, at a point 1·5 cm. distal to the origin of the left subclavian artery. It appeared to have extended for two-thirds of the circumference initially, but the medial tear had partly reunited, leaving only a recess in the intima to show its full extent. This remaining hole measured 1 cm. by 1·5 cm. in area, and had a smooth, endothelialized surface. There were two small round fenestrations beneath the first hole.

At the level of the first constriction there was a defect in the dividing wall 1·5 cm. in diameter, forming a communication between the aorta and the aneurysm. On the right lateral wall of the aorta, directly opposite this communication, there was a similar more recent intimal tear leading to a second smaller dissection, which extended 2 cm. in each direction. This cavity was flattened and endothelialized, and contained a small quantity of thrombus.

There was another small communication at the level of origin of the renal vessels. The terminal part of the aneurysm reentered the original circulatory channel at the aortic bifurcation, where the dividing wall acted as a partition allowing free flow from the aorta and the aneurysm into the common iliac vessels.

The wall of the aneurysm appeared to be endothelialized, and in places there were yellowish atheromatous plaques, while distally the wall was calcified. The saccular dilatations were filled with laminated thrombus. The intercostal and lumbar vessels were stripped from the aorta, but some appeared to arise from the aneurysm. The main arterial trunks had been completely spared. The original aorta had a smooth intima free of atheroma. In the upper thoracic and lower lumbar regions the adventitia was dense, possibly owing to organization of extravasated blood from the acute phase.

Histological Findings.—A section of the ascending aorta appeared normal, apart from fragmentation of elastic fibres. The aorta just proximal to the dissection showed a strip of external media separated from the rest by a fibrous layer, which was connected to the intima at one site owing to a complete defect in the media (Figure II). This probably represented a

FIGURE II

Case I. Aortic wall just proximal to the dissection. A large defect is seen in the elastica. A thin layer of external elastica is separated from the rest of the media by fibrous tissue. (Elastic tissue stain, ×40)

dissected zone which had healed and become completely organized. The media showed extensive loss of elastic fibres and numerous degenerate zones without nuclei. A section of the aneurysm showed similar changes in the media, and a thick fibrous layer covered by flattened endothelium which constituted a new "intima".

CASE II

The patient was a pensioner, aged 61 years, who had been a grocer. While walking on June 19, 1958, he suddenly was seized with a pain in the chest and tightness in the throat. These symptoms lasted only a few minutes, and he was able to walk to his car and drive home. As he felt generally weak and unwell, he went to bed. Next day he had a sudden choking sensation in the throat, lasting for an hour, but this passed off again quite rapidly. He remained in bed for two weeks and had only occasional attacks of breathlessness.

On July 22, 1958, while still in bed, he felt a hot, knife-like pain behind the sternum. It passed down into the abdomen and caused him to vomit. Some 12 hours later the pain dramatically disappeared. He had begun to lose weight, and had recurrent bouts of nocturnal dyspnœa. The discovery of a left pleural

effusion led to aspiration of 16 ounces of grossly blood-stained fluid. An X-ray film of the chest after this showed some residual fluid and a mediastinal mass at the site of the aortic arch. He was suspected of having a carcinoma of the lung, and was transferred to the Royal Adelaide Hospital on August 1, 1958, for investigation.

On examination of the patient, his blood pressure was 170/95 mm. Hg. No inequality of the radial pulses was detected. The heart was enlarged on clinical examination, and the sounds were regular and normal. There were signs of fluid at the base of the left pleural cavity extending to the sixth rib posteriorly. The abdomen was normal, and there were several discrete lymph nodes in the neck and both axillæ. Paracentesis thoracis yielded 10 ounces of dark blood-stained fluid. Microscopic examination of this fluid and repeated examination of sputum failed to reveal the presence of malignant cells. Biopsy of an axillary lymph node showed reactionary hyperplasia. The bronchoscopic findings were normal, apart from exaggerated pulsation below the arch of the aorta. An angiocardiogram showed that the mass was due to an aneurysm of the posterior portion of the aortic arch. The actual aneurysm appeared localized; but the ascending aorta before it and the descending aorta after it were remarkably unfolded.

On October 6, 1958, the patient underwent an operation for resection of the aneurysm and free grafting, under hypothermic anæsthesia. The aneurysm was dissected with difficulty, owing to a thick fibrous reaction surrounding it, but the acute dilatation was eventually demonstrated arising between the left common carotid and left subclavian arteries, and terminating some 6 cm. lower. The left subclavian artery arose from the wall of the sac. The aorta was clamped at the level of the left common carotid artery. When it was divided, it was obvious that the aneurysm was of the dissecting type, the incision passing through the primary intimal tear. The proximal end was trimmed back to the commencement of the dissection, and a free graft of nylon filter cloth was attached. The aneurysmal sac was excised, and the lumen of the dissection was obliterated by apposition of its walls, which were then sewn to the distal end of the graft. The left subclavian artery was ligated when adequate collateral circulation was demonstrated.

The patient did not fully recover consciousness after operation, and it was apparent that he had a left hemiplegia. He died 22 hours later.

Autopsy

At autopsy there was an extensive subarachnoid hæmorrhage over the right frontal and parietal regions. Examination of sections of the brain revealed a massive intracerebral hæmorrhage in the right frontal region, which had extended through the cortex to the meninges.

The left pleural cavity contained several ounces of heavily blood-stained fluid, and there were many recent vascular adhesions over the apex of the upper lobe of the left lung. The lung was normal on section.

The intact aorta is represented in Figure III, the acute dilatation between planes AA and BB being removed at operation and replaced by graft. Blood appears to have entered at the primary intimal tear, to fill the saccular aneurysm and then pass down in the aortic coats in a sheath-like dissection to end at the common iliac arteries.

The heart was enlarged and the left ventricle was hypertrophied. The ascending and transverse parts of the aortic arch were free of atheroma, but at the level of the left common carotid artery there was an abrasion where the aortic clamp had been applied. The whole thoracic aorta was surrounded by thick fibrous tissue resulting from organization of extravasated blood.

Below the graft, the true aorta was surrounded for two-thirds of its circumference by a dissecting aneurysm. The anterior third was spared, so that the mesenteric and renal vessels arose from normal aorta. The intercostal and lumbar vessels arose from the sac, and their corresponding openings in the aortic wall were largely obliterated; however, several of the lumbar openings were quite patent. The dissection

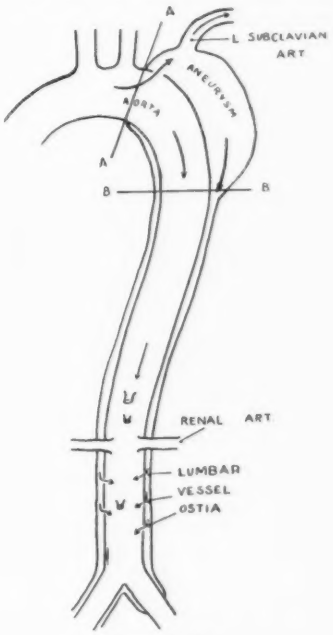

FIGURE III

Case II. Diagram of dissecting aneurysm before operation, with arrows showing the flow of blood through two channels

extended along the common iliac vessels, to end blindly on the left and probably similarly on the right, as no point of reentry was demonstrated. The lumbar orifices probably acted as sources of reentry for blood flowing through the aneurysm.

The intima of the true aorta was free of atheroma, except for a few smooth nodules surrounding the ostia of intercostal vessels and some scarring in the lower lumbar region. The size of the lumen suggested that most blood traversed the true aorta. The surface of the dissection was smooth and glistening, showing that some endothelialization had occurred. At various levels, fibrous strands passed from the aortic wall to the outer wall of the sac, forming a typical ladder-rung pattern. Their position did not correspond with intercostal vessels, and they appeared to be endothelialized remnants of frayed-out elastica from the media of the aorta (Weiss *et alii*, 1940).

Histological Findings.—The aorta proximal to the graft showed defects in the internal elastic lamina.

Throughout the media the elastic fibres were broken up, structureless gaps being left of what appeared to be altered ground substance, and there was a generalized paucity of nuclei. Cystic spaces characteristic of Erdheim's cystic medionecrosis were not noted.

The wall of the sac consisted of a thin layer of degenerate external media covered by a thick layer of acellular fibrous tissue, the surface of which was covered in parts by a few flattened endothelial cells, especially in the lumbar region.

In the aortic wall were a few intimal atheromatous areas. The media showed gross destruction of the elastic tissue, with a defect in one area extending almost the full thickness of the media. The external surface, which formed the inner wall of the aneurysmal sac, was composed of fibrous tissue with a thin endothelial covering.

CASE III

The patient was a butcher, aged 42 years, who was holidaying in the country. On September 11, 1957, he went to the toilet to use his bowels as usual, but on getting up he experienced a sharp stabbing pain in the substernal angle. The pain was severe and lasted all day. He was shocked, and had a mild fever, but breathing was not abnormal. He was placed in hospital with a diagnosis of myocardial infarction. Three days later, there was an exacerbation of pain in the right side of the chest. After two weeks he was transferred to Adelaide. His general practitioner found him in severe congestive cardiac failure, with a loud to-and-fro cardiac murmur and other signs suggesting aortic incompetence. The Wassermann reaction was negative. Digitalis therapy was commenced, and after a few weeks mercurial diuretics were given intramuscularly to combat the œdema of his ankles. Eight weeks after the initial "heart attack", he began to be short of breath, at first only on lying down; but this became more severe till eventually he was continually dyspnœic. There was no family history of heart disease. The patient had been discharged from the Army in 1945, quite well apart from a blood pressure reading of 210/110 mm. Hg.

When examined on December 9, 1957, he was pale, and acutely dyspnœic. There was clubbing of the fingers. The percussion note was dull at the bases of both lungs posteriorly, and there was a small pleural effusion on the right side. There were scattered crepitations in the same areas. The heart was considerably enlarged, and the apex beat was forceful and heaving. There was a loud to-and-fro murmur over the whole precordium. Both radial pulses were present; but the left common carotid artery was not pulsating freely, and a thrill could be felt above the left clavicle. The right femoral artery was pulsating more vigorously than the left. The blood pressure in the left arm was 160/60 mm. Hg, while that of the right arm was 115 mm. Hg systolic, the diastolic reading being undefined.

The patient was thought to have a dissecting aneurysm of the aorta following an initial intimal tear in September, 1957—his "heart attack". During the ensuing months his illness was characterized by exacerbations and remissions of congestive cardiac failure, although he was left progressively worse at the end of each attack. A course of thiouracil was given to reduce his circulatory requirements, but there was no improvement. He often complained of severe abdominal pain, and at one time transient frank hæmaturia occurred. With increasing œdema mercurial diuretics were given daily, and eventually multiple stab wounds were resorted to in an attempt to relieve his water-logged limbs. Over the last two weeks profuse diuresis occurred, and the patient then became oliguric and irrational, with a dry tongue and complete anorexia. He died on February 9, 1959, 17 months after the initial attack.

Autopsy

The relative findings at autopsy included an old dissecting aneurysm of the double-barrelled type; an enlarged heart, mainly involving the left ventricle; a hypertrophied right kidney and a contracted left kidney; bilateral pleural effusions of 60 ounces of straw-coloured fluid; generalized congestion of viscera, especially the lungs, liver and spleen (Figure IV).

The following description applies to the preserved specimen. The heart was considerably enlarged, and when sections of the left ventricle were examined, was seen to be both dilated and hypertrophied. The aortic valves were normal, but the valve ring was dilated so that five fingers could be admitted readily. There was considerable atheroma in the left coronary artery.

One centimetre above the aortic valves there was a transverse tear in the intima, extending almost the full circumference of the aorta. The intimal tear led into a dissecting aneurysm, which extended the full length of the aorta, at first on the postero-superior aspect of the arch, then swinging on to the anterior surface. The dissection had extended proximally to reach the right coronary artery, but did not occlude it, while the left one was intact. The intima thus formed a cuff above the aortic valves. The dissection extended around almost three-quarters of the circumference of the aorta, leaving a narrow strip of intact wall on the under side of the arch and down the right anterior surface of the descending aorta. The first part of the aneurysm was formed by a saccular dilatation, but the remainder was of fairly uniform bore, forming a typical double-barrelled aorta. The dissection terminated at the bifurcation of the left common iliac artery as a blind cul-de-sac which contained old clot; on the right it extended 10 cm. along the external iliac artery, where it ruptured back into the normal arterial channel, the thin dissected segment acting as a dividing membrane between the two streams.

The wall of the dissecting aneurysm had become endothelialized with a smooth, finely crinkled surface. There were dozens of smooth fibroelastic strands running transversely, connecting the inner to the outer wall of the dissection, and occurring most plentifully in the upper thoracic region. The aortic wall was also smooth except in the abdominal aorta, which was the seat of moderate atheromatous changes.

The dissection had extended a short distance up the walls of the innominate, left common carotid and subclavian arteries, forming a sleeve, and these also had become endothelialized, and possessed transverse fibroelastic strands. A hæmatoma had formed in the space around the left common carotid artery, constricting the lumen. Blood could flow through both channels in the other vessels.

The left-sided intercostal vessels were stripped off the aorta and arose from the aneurysm. The cœliac and superior mesenteric vessels straddled the margin of the dissection, so that the lumen for each vessel was directly continuous with the aorta, but there was a short dissection up the left side of each. The inferior mesenteric artery was torn from the aorta and arose from the false passage.

There were two arteries of normal calibre passing to the right kidney, which was hypertrophied, measuring 12 by 7 cm. The capsule peeled readily, leaving a smooth surface. The left renal artery was smaller and

arose from the aneurysm. It had a narrow lumen, which appeared to be completely occluded at a distance of 1 cm. from its origin. The left kidney was contracted, measuring 6 by 2 cm., with capsule and perinephric tissue adherent. The surface was coarsely granular and had several large depressions. Examination of sections revealed multiple old infarcts, very little functioning renal tissue being left. The arteries were not prominent and the pelvis was not thickened.

Histological Findings.—There was some fragmentation of elastic tissue of the media, but the main defect appeared to consist of circumscribed areas completely devoid of nuclei. The smooth muscle in these zones had degenerated. There were a few clefts between muscle layers where the ground substance appeared foamy, and occasional microcysts were present. There was a flat endothelium covering the thick fibrous layer which lined the aneurysmal cavity between the split media.

The left kidney showed large areas of infarction where the glomeruli and tubules were represented by eosinophilic masses. In the small zone of surviving renal

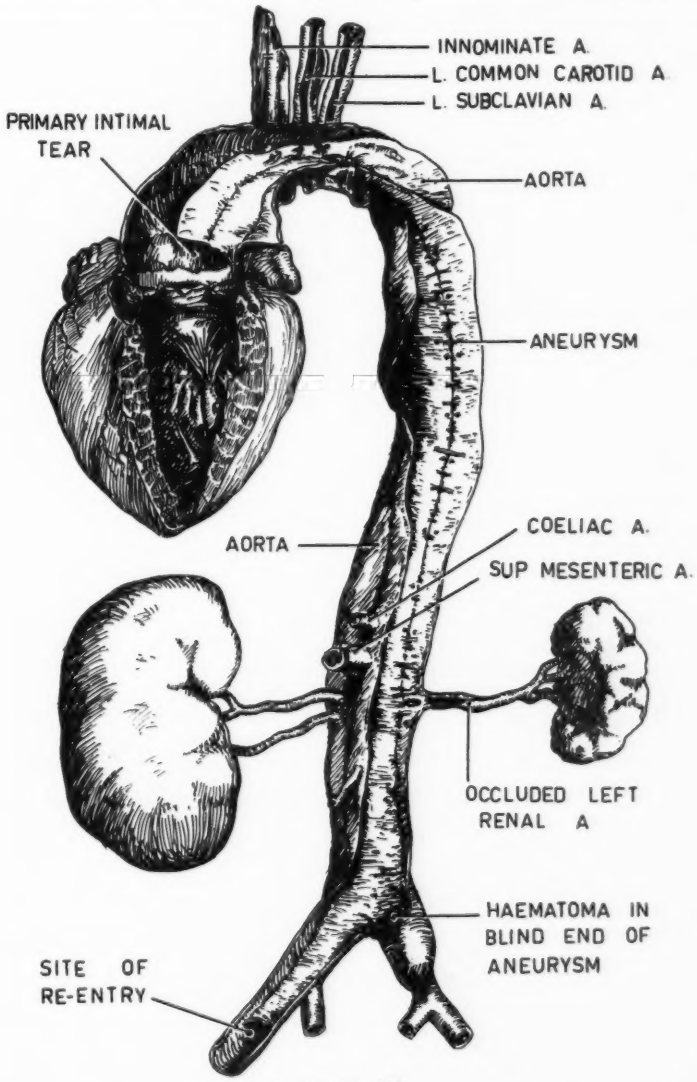

FIGURE IV

Dissecting aneurysm in Case III, showing dilated left ventricle, hypertrophied right kidney and atrophied left kidney

tissue, the glomeruli showed marked crowding from tubular atrophy. There was no marked evidence of hypertension or pyelonephritis.

DISCUSSION

The first two cases have several points in common — namely, the onset during mild exertion, external leakage into the pleural cavity, a similar site of primary intimal tear and a long sheath-like dissection which had undergone endothelialization. The mesenteric and renal vessels were spared. Had these two patients died in the acute phase, as is often the case, the diagnosis would not have been made, for it was only by investigation of what was considered primary lung disease that the true nature of the lesion was made out.

Case I demonstrates convincingly that the establishment of a double-barrelled aorta is compatible with symptomless existence, but does not confer immunity from further catastrophe. In his analysis of 300 cases from the literature, Shennan (1934) found 79 cases of "healed" dissection; 16 of the patients died from hæmorrhage into one of the cavities and 34 from heart failure.

In Case II the dissected sac was found to be completely endothelialized only 15 weeks after the initial tear. The thick fibrous layer beneath this endothelium may well represent organized thrombus lining the walls of the sac. The patient's left subclavian artery, arising from the acute saccular dilatation, probably drained most of the blood from the aneurysm, leaving only a small residuum to pass down the walls of the aorta to reenter via the foramina where lumbar vessels had been torn from the aortic wall, as the dissection appeared to end blindly.

In Case III the acute onset of pain in the chest followed by unequal peripheral pulses made the diagnosis of dissecting aneurysm more obvious. The flapping cuff of proximal intima, and the pressure of retrograde flow during diastole, soon caused dilatation of the aortic valve ring and incompetence. Occlusion of the left renal artery led to almost complete infarction of that organ, with transient hæmaturia. The right kidney is a good example of work hypertrophy. There was no evidence of hypertensive vascular changes, so that the pressure recorded in 1945, on the patient's discharge from the Army, was probably not typical. One wonders what might have been the blood pressure change following this unilateral renal ischæmia, had the aortic incompetence not developed. The complaint of abdominal pain could be attributed to partial obstruction of the mesenteric vessels at their origin from the aorta.

Weiss *et alii* (1940) considered that the likelihood of healing and endothelialization was about one in 10 dissecting aneurysms. The present three cases came from a series of 42 dissecting aneurysms found in some 6000 autopsies performed at the Royal Adelaide Hospital during the past 10 years. From the nature of the disease, many patients are likely to expire before admission to hospital, and consequently the healing incidence is probably a good deal less than 10%. It is of interest that there were 17 acute dissecting aneurysms of the aorta amongst approximately 2800 autopsies performed in the coroner's department for the same period. These were found in people who had died suddenly and unexpectedly.

ACKNOWLEDGEMENTS

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DISSECTING ANEURYSM OF THE AORTA

HISTOLOGICAL APPEARANCES AND AN HYPOTHESIS OF PATHOGENESIS[1]

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SUMMARY

Comparison of the histological appearances of the aorta from 38 subjects of dissecting aneurysm and of a small series of aortas from control subjects revealed no characteristic histological abnormality accompanying aortic dissection. Alterations involving one or more elements of the media were present in a number of cases, but similar changes were seen in control subjects. In a substantial proportion of cases of dissecting aneurysm the aortic wall was of normal appearance.

These histological findings are contrasted with the gross change in resistance to "splitting" forces demonstrable macroscopically in many cases of aortic dissection.

It is postulated that the underlying medial defect predisposing to aortic dissection is a generalized and reversible one, involving fine collagen fibres and the intercellular substance of connective tissue. The clinical, macroscopic, histological and experimental aspects of the disease are discussed in relation to this hypothesis.

DISSECTING ANEURYSM of the aorta or large elastic arteries has been known since ancient times, and the following macroscopic features of the condition are generally agreed upon. A hæmatoma lies within the media, commonly originating in the ascending aorta or arch, and may extend the whole length of the aorta; an intimal tear is present in the majority of cases, but in about 10% the intima is intact, the blood in these cases at least arising from vasa vasorum. Death commonly occurs rapidly from external rupture of the hæmatoma; but in a proportion of cases long-term survival with the formation of a "double-barrelled" aorta occurs.

It has been accepted since the work of Peacock (1843) that the primary abnormality in the aortic wall involves the media; but a wide variety of histological changes of a degenerative type affecting one or more connective tissue elements has been held to be the essential lesion of the disease. Many of these have been labelled "medionecrosis idiopathica cystica", a term first used by Erdheim (1930); he, however, reported two cases of rupture of a saccular aneurysm of the ascending aorta occurring without dissection. Study of the literature reveals that much of this confusion is due to the circumstance that while a very large number of papers on dissecting aneurysm has been published, descriptions of any considerable number of cases in which the aortic wall has been adequately studied histologically are few. The clinical records and pathological specimens from a considerable number of cases are available in Melbourne; the clinical and macroscopic features of these have already been recorded (Hurley and Birrell, 1956), and in the present paper the histological appearances in the aortic wall are described and compared with a small series of aortas from patients who died from causes unconnected with their aortas. On the basis of the appearances seen, an hypothesis of the pathogenesis of aortic dissection is advanced.

MATERIALS AND METHODS

Specimens were examined from 38 cases of dissecting aneurysm, all clinically falling into the most common group of cases—those occurring in middle-aged or elderly people, usually in association with arterial hypertension (Hurley and Birrell, 1956).

In 28 cases, from one to three blocks were taken from the ascending aorta or arch of the aorta, and in the remaining 10 cases multiple blocks from the whole length of the aorta were examined.

The normal aortas were from two sources; the "young" group were blocks taken from the arch of the aorta in 12 young subjects who had died suddenly or accidentally and were examined by the City Coroner's Department, Melbourne; and in the "old" group, blocks from the same area were obtained during 10 routine autopsies at the Royal Melbourne

[1] Received on June 26, 1950.

[2] Senior Lecturer.

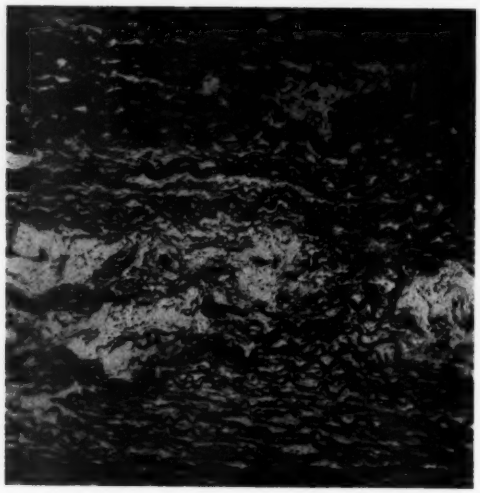

FIGURE I

Photomicrograph of media of aorta from a subject of dissecting aneurysm, showing large irregular elastic tissue defects. (Weigert's elastica, ×80)

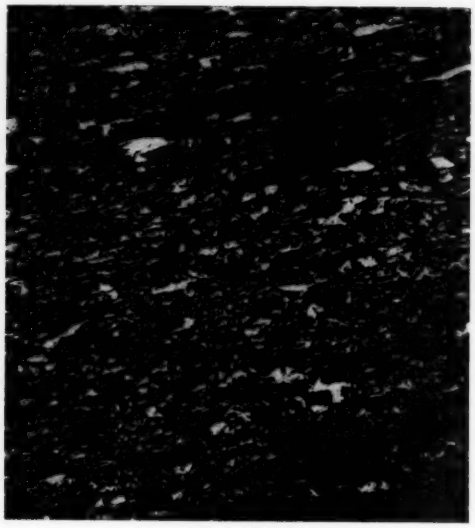

FIGURE II

Photomicrograph of media of aorta from a middle-aged "control", showing minor breaks in elastic tissue lamellæ. (Weigert's elastica, ×80)

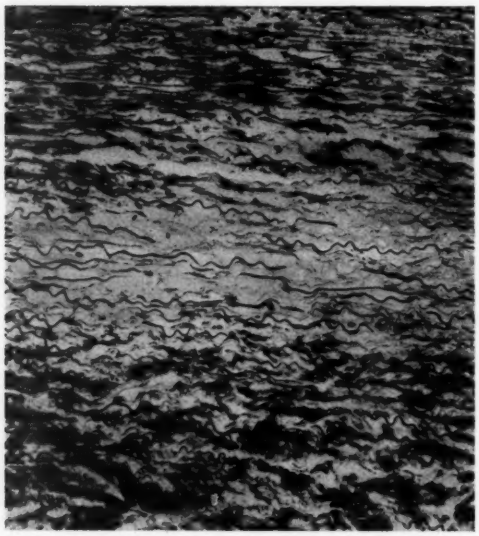

FIGURE III

Photomicrograph of media of aorta from a middle-aged "control", showing large laminar area of loss of smooth muscle. Note preservation of elastic lamellæ. (Picro-Gomori, ×80)

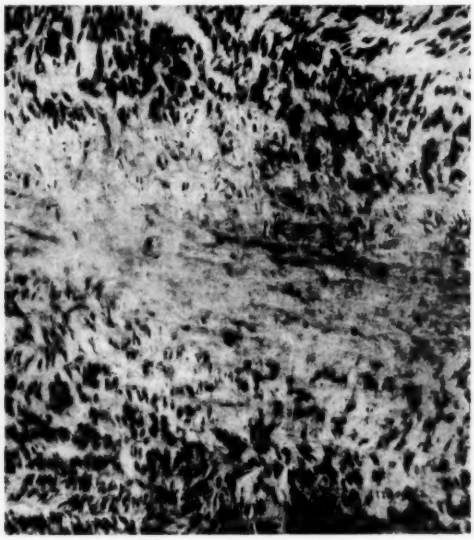

FIGURE IV

Photomicrograph of media of aorta from a subject of dissecting aneurysm, showing large laminar area of loss of smooth muscle. Note preservation of pattern of elastic lamellæ. (Picro-Gomori, ×120)

Hospital in cases of death from causes other than dissecting aneurysm in patients aged over 45 years.

Material from all three groups was embedded in paraffin and sections were cut at a thickness of 7μ. The following stains were used: hæmatoxylin and eosin, Van Gieson, Picro Gomori, Weigert's elastic tissue, silver impregnation for reticulin (Lillie, 1948), Alcian blue, toluidin blue, periodic acid Schiff and Hale's colloidal iron (Rinehart and Abdul-Haj, 1951).

RESULTS

It is convenient first to describe the appearances seen in the different components of the aortic wall, and then to set out in detail the incidence of the various changes seen in the subjects examined.

CHANGES OBSERVED IN COMPONENTS OF THE AORTIC WALL

Intima

The intima of the aorta increases progressively in thickness with age. Consequently, in all the present cases of dissecting aneurysm and the normal "old" aortas, a considerable thickness of loose connective tissue containing various types of connective tissue cells and both collagenous and elastic fibres was present between the surface endothelium and the media. In the "young" group this layer was much thinner.

In a proportion of cases atheroma, ranging from early to severe lesions, was present. This was of the usual form, and will not be described in detail; but dilated capillaries were a prominent feature in the more advanced lesions. This will be discussed later.

Media

1. *Elastic Tissue.*—Four types of alteration were seen in elastic tissue: (i) Elastic tissue loss associated with general medial thinning deep to large atheromatous patches, the normal pattern of the media being preserved. (ii) Large elastic tissue "faults" with gross disruption of the regular lamellar arrangement. This was always associated with loss of the normal orientation of muscle cells (Figure I). (iii) Small scattered defects involving one or two lamellæ without interference with normal medial pattern (Figure II). (iv) Disruption and fraying of a few fibres in immediate relation to intramedial dissection, the damage being clearly a mechanical result of the process of dissection.

2. *Muscle.*—Three types of lesions were seen in muscles: (i) Muscle loss associated with generalized thinning deep to an atheromatous patch, corresponding to the loss of elastic tissue described in 1 (i) above. (ii) Laminar areas in the media of loss of the normal staining of muscle nuclei, to produce structureless areas of more or less uniform staining in hæmatoxylin and eosin preparations. In most of these areas considerable intercellular substance could be demonstrated by special staining, but others maintain the normal tinctorial characters of muscle cells. In the areas of muscle loss the elastic lamellæ were still present and stained normally, but sometimes appeared more crowded together than usual (Figures III and IV). (iii) Focal areas of loss of muscle nuclear staining similar in type to (ii), but without the laminar form. These areas varied from loss of a few muscle cells to extensive areas of nuclear loss (Figures V and VI).

3. *Intercellular Substance.*—Two types of change were seen in intercellular substance: (i) A generalized diffuse increase throughout the media. Minor degrees of this change are most difficult, or even impossible, to distinguish, as the amount of stainable intercellular material varies widely in different normal aortas (Braunstein, 1958), and is dependent on a number of technical factors (see below). (ii) Focal increase in intercellular substance in association with areas of muscle or elastic tissue loss (Figure VII). In both types, whenever a sufficiently large area of intercellular substance was present, it appeared finely cystic on examination with the high power of the microscope (Figures VIII and X).

4. *Vessels.*—In the normal aorta, vasa vasorum are confined to the outer one-third of the media. In this series the alterations seen were in distribution only—in no case did the vasa vasorum appear abnormal in form. Two types of change in distribution were seen: (i) In cases accompanied by severe atheroma, vessels were present throughout the whole thickness of the media, and the intima was also widely vascularized. (ii) In some cases, with no local atheroma, vessels penetrated further into the media than usual. In several cases free red blood cells were seen between medial lamellæ well in advance of an acute dissection, but the adjacent vasa vasorum appeared normal.

DISTRIBUTION OF THE ABNORMALITIES SEEN

The distribution of the abovementioned lesions in both the 38 dissecting aneurysms and the two series of control aortas is shown in Tables I, II and III.

Several points contained in the tables require emphasis and discussion. First, whilst some abnormality of the media was present in 17

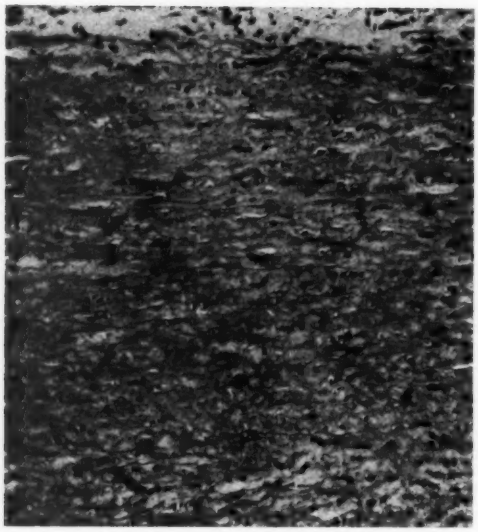

FIGURE V

Photomicrograph of media of aorta from a young "control" subject, showing variation in distribution of muscle cell nuclei and small areas of loss of muscle. Note the considerable quantity of intercellular substance visible throughout. (Hæmatoxylin and eosin, ×120)

FIGURE VI

Photomicrograph of media of aorta from a young "control" subject, showing irregular areas of loss of muscle in media just beneath intima, without laminar formation. Note large amount of intercellular substance visible. (Picro-Gomori, ×80)

FIGURE VII

Photomicrograph of media of aorta from a subject, of dissecting aneurysm, showing focal accumulations of intercellular substance associated with loss of muscle cells. (Hæmatoxylin and Alcian blue, ×180)

FIGURE VIII

Photomicrograph of media of aorta from a young "control" subject, showing "cystic" appearance of intercellular substance, most marked in a focal accumulation beside a vasa vasorum. (Hæmatoxylin and Alcian blue, ×120)

cases of dissecting aneurysm, no lesion was found in the majority, 21 cases. Secondly, of the several medial abnormalities found in cases of dissecting aneurysm, only one, a major elastic tissue defect, was not also present in a proportion of the control series. This is most apparent in the case of muscle defects, either the focal or

FIGURE IX

Photomicrograph of portion of wall of aorta from a subject of dissecting aneurysm, showing large elastic tissue defect filled with intercellular substance producing appearance similar to " medionecrosis cystica ". (Hæmatoxylin and Alcian blue, ×22)

the laminar form of which was present in 17 of 38 cases of dissecting aneurysms and in 12 of 22 cases in the combined control series; but both minor elastic tissue defects and focal accumulation of intercellular substance in relation to muscle and elastic tissue defects were also found in both aneurysm and control cases. In one of the two instances in which major elastic tissue defects were seen in cases of dissecting aneurysm, sufficient intercellular substance was present in the lesion to produce a cyst, easily seen on examination of the aortic wall with the low power of the microscope (Figure IX). This was the only example in the whole investigation of a lesion resembling medionecrosis cystica as described by Erdheim (1930). On high-power microscopic examination, the material within this cyst was itself finely " cystic " in appearance (Figure X).

The significance of the slight generalized increase in intercellular substance seen in eight cases of dissecting aneurysm is doubtful. The amount of such material visible varies widely in different individuals (Braunstein, 1958), and the quantity seen depends also on the time between death and fixation of the aorta. This was clearly demonstrated in a case of dissecting aneurysm occurring in a patient with Marfan's syndrome (Hurley, 1959), in which much more intercellular material was present in specimens taken at autopsy than in operative biopsy material. Similar and more rapid autolytic change occurs in the rat aorta (Menzies and Mills, 1957). As some degree of autolytic change is inevitable in all human autopsy material, the interpretation as abnormal of minor generalized changes in intercellular substance is of very doubtful validity.

The striking change in medial and intimal vascularity in six of the aneurysm cases and in one " old " control is clearly related to atheroma, and was not seen in the absence of severe intimal disease; its greater frequency in the cases of

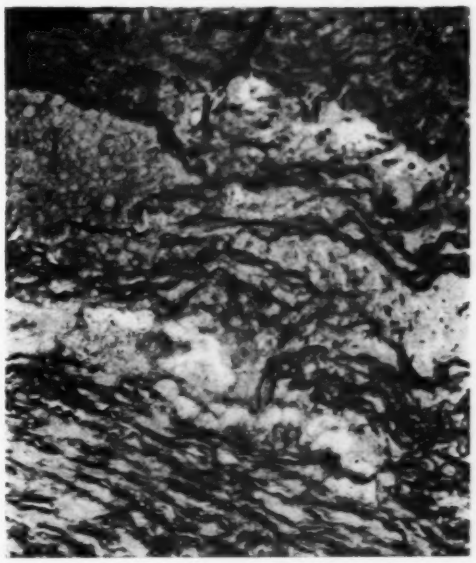

FIGURE X

Photomicrograph of portion of area of media shown in Figure IX, showing finely " cystic " appearance of intercellular substance in area of " medionecrosis cystica ". (Hæmatoxylin and Alcian blue, ×180)

dissecting aneurysm reflects the larger number of cases of severe atheroma present in this group. It should be stressed that such vascularity was seen in only a small proportion—six of 38 cases—of the dissecting aneurysm series.

In summary, in more than half the cases of dissecting aneurysm no abnormality was found,

and of the changes present in the remainder all except one, present in two cases only, were also seen in control cases. From this it must be concluded that by the methods used in this series, no histological abnormality of the aortic media can be consistently related to the occurrence of dissecting aneurysms.

TABLE I

Changes Seen in Aortic Wall in 38 Cases of Dissecting Aneurysm

Component of Wall	Lesion Seen	Number of Cases	Comment
Intima ..	Normal	23	
	Atheroma	15	
	Severe .. 8		
	Early .. 7		
Media:			
Elastic tissue	Normal	28	10, despite laminar muscle loss 4, with recent dissection in block
	Loss accompanied by general medial thinning[1]	6	All with severe atheroma
	Large "faults" ..	2	
	Scattered small defects	2	One "double-barrelled" aorta
	"Tears" near acute dissection	3	
Muscle ..	Normal	15	
	Loss with general medial thinning	6	All with severe atheroma
	Laminar loss ..	10	
	Focal loss	7	
Intercellular substance	Normal	21	
	Focal increase with muscular or elastic defect	9	
	Generalized increase	8	
Vessels ..	Normal	27	
	Vascularization to intima with atheroma	6	
	Vessels increased in outer half of media	3	Free erythrocytes in media in one case
	Vessels whole media without atheroma	2	Free erythrocytes in media in one case

[1] In three cases more than one type of elastic tissue lesion was present.

DISCUSSION

COMPARISON WITH PREVIOUSLY RECORDED SERIES

Published accounts of the appearances of the aortic wall in dissecting aneurysm contain numerous records of one case or a small series of cases and a number of reviews, but there are relatively few papers reporting detailed studies of any considerable number of cases.

The findings of Gore and Seiwert (1952) and of Gore (1952) are widely accepted as a description of the histological basis of aortic dissection. These authors described the histological appearances seen in 72 cases of dissecting aneurysm from the files of the Armed Forces Institute, and Gore (1952) discusses the pathogenesis of the disease based on the same material. The number of blocks taken from each aorta is not stated, and whilst the PAS technique was employed, special stains for the mucopolysaccharides of the intercellular substance such as Alcian blue, toluidine blue or Hale's colloidal iron were not used. Gore and Seiwert (1952) report that "in each of the aortas examined microscopically a focal degenerative process was observed at multiple sites in the media", and describe two forms of degeneration primarily affecting muscle and elastic tissue respectively. The changes seen in both forms are well illustrated and are very like the appearances in the present series.

TABLE II

Number of Cases of Dissecting Aneurysm in which Medial Abnormality Found

Condition of Media	Number of Cases
No abnormality	21
One or more of changes listed in Table I (excluding atheroma)	17
Total	38

TABLE III

Summary of Findings in Normal Aortas

Tissue	Comment
"Young" Group (12 Cases)	
Intima	Normal in all
Media:	
Muscle	Acellular areas in 6 cases, laminar in 1 only
Elastic tissue ..	Normal—11 cases. Multiple small defects in 1 case
Intercellular substance	Considerable amount in all, most in intima and inner media "cystic" whenever large enough accumulation
Vessels	Confined outer third of media in all
"Old" Group (10 Cases)	
Intima	Atheroma, 5 cases—3 early, 2 severe
Media:	
Muscle	Areas of loss in 6, 3 focal, 3 laminar—2 small, 1 large
Elastic tissue ..	No defects seen
Intercellular substance	Normal amount—more in acellular areas of media where finely "cystic"
Vessels	Confined to outer third of media in 9 cases. Full thickness media, 1 case, with associated atheroma

Two other changes described by these authors are less convincing. They are not apparently aware of the importance of mucopolysaccharides in the structure of the normal aorta, and hold that "in no instance was chromatotrophic substance observed in the absence of medial degeneration . . . and accordingly the appearance of mucin on this basis alone warrants considering it a reactive phenomenon". At another point, the intercellular material is

called myxomatous—a description which was regarded as inaccurate by Bunting and Bunting (1953), and for which there is no support in the present series. A process is also described of medial vascularization by thin-walled vessels "supported essentially by the surrounding defective media"; this description and the illustrations provided closely resemble normal vasa vasorum, and it is perhaps important that these authors report no concurrent study of normal aortas.

To summarize the findings of Gore and Seiwert (1952), elastic tissue degeneration was seen in 16 cases, muscle lesions were found in 36, and both were present in 20. The extent of the lesions is unknown and the number of blocks studied is not stated. The authors recognize that "it is not possible to distinguish the muscle variety of medial degeneration in dissecting aneurysm from the one which accompanies aging", and give several references to muscular changes in elderly people without dissecting aneurysm, but conclude on no stated evidence that degeneration is more extensive in the cases in which dissection has occurred. A second interpretation of these findings is that in not less than 36 of 72 cases no abnormality not commonly found in the absence of dissection was seen in the aorta.

The standard reference in British literature is the exhaustive review by Shennen (1934). From a very lengthy description the findings may be summarized as follows: "All the cases showed important microscopic changes in the media—degeneration . . . of the elastic lamellæ, atrophy and fatty change in muscle, . . . and in all there was hyaline degeneration of the connective tissue either of the sclerotic type or with swelling and vacuolation . . . in all cases marked degeneration of the delicate elastic and connective tissue fibres passing between the laminæ." The importance of Shennen's (1934) paper was to emphasize that the essential change in dissecting aneurysm lay in the media at a time when atheroma was widely considered the major cause of the disease; but his histological descriptions are difficult to interpret. This paper was written long before any of the more recent work on the importance and composition of intercellular substance.

Two most valuable papers are those of Rottino (1939*a*, 1939*b*); the first records the appearances in 12 cases of dissecting aneurysm, in which the whole aorta from its origin to the distal end of the arch and representative blocks from that level to its termination were carefully studied; and the second records the results of a similar study of 210 aortas removed at routine autopsy.

The results may be summarized as follows: (*a*) Laminar muscle loss as described above was seen in 10 of 12 cases of dissecting aneurysm and in 92 of 210 routine autopsies. In the latter group it occurred more commonly in association with arterial hypertension. (*b*) Elastic tissue damage of varying degree was present in eight cases of dissecting aneurysm and in eight normal aortas. In both groups it was commonly associated with local accumulation of intercellular substance. (*c*) Except for laminar muscle loss in the descending aorta in one case, all changes seen in association with dissecting aneurysm were confined to the ascending aorta and arch, and often to a small region in the proximal part of the ascending aorta only.

Two conclusions may be drawn from these studies: (i) Laminar muscular medial degeneration is of no significance in the ætiology of dissecting aneurysm. This is important in respect of the findings of Shennen (1934) and of Gore (1952) discussed above. (ii) The changes seen in cases of dissecting aneurysm may be causally associated with the intimal tears present in that region of the aorta in all Rottino's cases; but no change was seen in any case to account for more distal spread of dissection, which was presumably present although its extent is not stated in the paper.

The two earliest authors to claim specific changes in the aortic media related to dissecting aneurysm were Gsell (1928) and Erdheim (1930). Gsell (1928) described six cases, and stated that the primary lesion was a necrosis of smooth muscle with subsequent fibrous replacement; his Figures 2 and 4 clearly depict the laminar acellular areas of muscle shown by Rottino to occur commonly independently of dissecting aneurysm. Erdheim (1930) described a lesion he termed "medionecrosis idiopathica cystica", and this is usually quoted as the histological basis of aortic dissection. In fact he described in detail two cases of ruptured saccular aneurysm without dissection, and the cysts were visible macroscopically. The changes found were confined to the wall of the aneurysm, although he made a most careful study of the whole aorta in both his cases.

By contrast, several papers report cases in which little or no abnormality was detected in the aortic wall. Glendy, Castleman and White (1937) recorded 19 cases, 13 of acute dissection, in eight of which lesions resembling Erdheim's medionecrosis cystica were seen in varying degree, but no lesion was seen in the remaining 11 cases. Bauersfield (1947) found no significant medial abnormality in any of 15 subjects he examined. Macleod and Williams (1956), in a study of 10 cases for comparison with a dissecting

aneurysm occurring in a patient with Marfan's syndrome, in which severe degenerative changes of elastic tissues were seen, found " similar changes in cases of dissecting aortic aneurysm were comparatively mild, and in eight of the 10 specimens of aorta remarkably slight ".

In summary, therefore, of this incomplete review of an extensive literature, there is evidence that in many cases the normal changes that accompany aging have been described as the causative lesion of dissecting aneurysm, and in others the degree and more particularly the extent of any abnormalities seen are doubtful. Conversely, in many cases, like those analysed in this paper, little significant abnormality was found.

In a recent report of cases of aortic dissection occurring in association with Marfan's syndrome (Hurley, 1959), a similar absence of histological change of a degree sufficient to account for the gross macroscopic abnormality was found.

An Hypothesis of the Pathogenesis of Aortic Dissection

By contrast with the minor histological changes, there is abundant evidence that gross change in the mechanical properties of the aortic wall accompanies dissection. Morgagni (1760), describing one of the first cases on record, states :

> It was observed that the external coat could be easily drawn away from the trunk and branches thereof, just as if it had been, for a long time, macerated in water.

Henderson (1843) reports :

> The outer coat with an adhering lamina of the middle, having admitted of being detached with a facility not much less than that with which two moist pieces of paper may be separated.

Less graphic reference to similar states of the aortic wall has been made by Babes and Mironescu (1910), by Shennen (1934) and by Gore (1953), who states :

> Medial degeneration in one case was so far advanced that mere manipulation sufficed to split the media into inner and outer portions throughout the aorta to its bifurcation, although the actual tract of hæmorrhage did not extend beyond the arch.

In this case only the muscular type of medial defect was present. I have myself seen a similar phenomenon, not occasionally, but in the majority of dissecting aneurysms examined in the fresh state.

Halliday and Robertson (1946) and Robertson and Smith (1948) measured the pressure necessary to produce spread of fluid injected into the aortic media from 46 routine autopsies, and found the pressure required to be greatly in excess of arterial blood pressure, the mean pressure being 560 mm. Hg. Milazzo (1952), repeating a test first devised by Cleland (1951), measured the force necessary to " peel " a normal aorta into layers, and found that " at no level in the media is there a significant upward or downward trend in the resistance to separation of the layers ". Wartman and Laipply (1949) injected blood into the aorta and main arteries of the dog, and found the hæmorrhages produced did not enlarge, and dissecting aneurysm did not result.

The autopsy and experimental observations taken together make it certain that some gross and widespread alteration in the mechanical properties of the aortic wall, far exceeding in degree and distribution the observed histological abnormality, is present in many, probably all, cases of dissecting aneurysm.

There are several observations providing evidence of the possible nature of this abnormality.

1. Dissecting aneurysm is a common complication of Marfan's syndrome—a relatively rare hereditary disturbance of connective tissue (Hurley, 1959). The precise nature of the defect is not known ; but there is evidence of quantitative abnormality of serum mucoproteins (Bacchus, 1958) and of increased urinary excretion of hydroxyproline (Sjerdsma, Davidson, Udenfriend and Mitoma, 1958). As this amino acid is practically confined to collagen, this indicates that collagen metabolism is abnormal in Marfan's syndrome.

2. Apart from cases occurring in association with Marfan's syndrome, dissecting aneurysm occurs in young people in only two conditions—in association with pregnancy and with coarctation of the aorta. In pregnancy there is known to be widespread alteration in the mechanical properties of connective tissue involving both collagen and ground substance (Storey, 1957) ; whether this is due to relaxin (Hisaw and Zarrow, 1950) or to ovarian hormones, or to both, is uncertain.

Coarctation is a disease with a strong male preponderance. Taussig (1947) comments :

> The condition is rare in women of normal physical development but occurs frequently in women with ovarian agenesis.

The mechanism here is completely obscure, but presumably hormonal in nature.

3. The only means of regularly producing in experimental animals dissecting aneurysm, along with widespread abnormalities of connective tissue, is by feeding them the garden

sweet pea, *Lathyrus odoratus*, its toxic component, β-aminopropionitrile, or related chemicals. By this means aortic dissection closely resembling the human disease can be produced in a number of animal species. The available evidence suggests that the mode of action of these compounds is to cause a delay in collagen synthesis, the delay being limited to a short period during collagen maturation (Hurley and Ham, 1959).

There are several differences, such as widespread associated lesions of connective tissue and its occurrence only in growing animals, between the experimental and human diseases, but the foregoing findings provide evidence of the type of connective tissue defect that may precede aortic dissection.

Taken together, all these observations suggest that a disturbance in the metabolism of collagen, perhaps involving also the closely related connective tissue ground substance, may be the basic defect underlying aortic dissection. The observation that the disease in young women is confined to pregnancy suggests further that the defect must be a reversible one. Much of the collagen present in the aortic wall is in the form of fine reticular fibres binding adjacent laminæ together, and there is evidence that such fibres and their related ground substance are metabolically highly active tissue (Slack, 1959), by contrast with the relatively inert elastic tissue of the aortic wall (Slack, 1955). Metabolically active tissue is much more likely to be subject to the postulated type of generalized reversible change.

All the foregoing findings are consistent with the basic abnormality underlying aortic dissection being an alteration in the metabolism of fine collagen fibres and of related connective tissue ground substance, of a type producing alteration in the physical properties of the aortic media, commonly affecting the whole or greater part of its extent, and not detectable by current histological techniques. In pregnancy and coarctation of the aorta there is evidence of a hormonal ætiology for the connective tissue defect, in Marfan's syndrome the defect is certainly degenerative, in experimental lathyrism the cause is a known toxin ; but in the common form of the disease, that occurring in middle age in association with arterial hypertension, although the physical change of the media is certainly present, there is no evidence of the cause of the connective tissue changes responsible for it. There is no evidence that, either in man (Pickering, 1955) or in experimental animals (Magarey, 1957) hypertension of itself can produce the type of change postulated, and the raised pressure probably merely results in dissection occurring in the presence of lesser degrees of an abnormality due to some other cause.

ACKNOWLEDGEMENTS

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STUDIES OF FAT METABOLISM IN ATHEROSCLEROSIS BY ISOTOPIC METHODS[1]

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SUMMARY

An isotopic lipid tolerance test is described. An assessment of this test on 40 patients with abnormal lipid metabolism and 12 controls has given the following results: (i) I^{131} glyceryl trioleate is a satisfactory tracer of lipid metabolism. (ii) The results of the test are consistent and reproducible. (iii) Patients with coronary atherosclerosis show raised lipid blood radioactivity levels during the first few hours, and these persist to 72 hours, when there is more complete separation between atherosclerotic and normal subjects. (iv) The lipid clearance time is prolonged in almost all patients with coronary heart disease. (v) The results give further support to the apparent linkage of atherosclerosis and disordered lipid metabolism. (vi) The lipid tolerance test described gives a method of assessing the degree of lipid metabolic disorder.

THERE is much evidence to show that in some individuals an abnormality in lipid metabolism plays an important part in the ætiology of atherosclerosis (Thannhauser, 1952; Dock, 1950). With this in mind, Becker *et alii* (1949), among many others, attempted to elaborate a type of lipid tolerance test to aid in the control and management of this disease. Such tests have involved the use of turbidometric methods. They suffer from the disadvantage that they may be carried on only over a period of a few hours, and during this time it is difficult to distinguish between the effects of gastric absorption and lipid metabolism.

We have developed a method based on the use of lipids labelled with radio-isotopes which, on account of its simplicity, may lead to a practical test for clinical use. The basis of the method will be discussed in this paper and our initial results reported.

METHODS

The material used in this test was I^{131}-labelled glyceryl trioleate (" Raolein "), and was obtained from Abbott Laboratories through the Commonwealth X-Ray and Radium Laboratory. This material has already been used by Ruffin *et alii* (1956) in the study of gastro-intestinal absorption.

In order to prevent any thyroidal retention of the radio-iodine released during the test, all subjects received three grains of potassium iodide three times daily, starting 24 hours before the test and continuing for four days.

The radioactive test meal was prepared as follows.

An oil-water emulsion was first made by vigorously stirring 40 ml. of peanut oil and 10 ml. of gum acacia in a mixer and then adding 20 ml. of water and agitating the whole until a stable emulsion was formed. A radioactive emulsion was prepared by taking 20 μc. per patient of the I^{131} glyceryl trioleate. This was poured into a stoppered flask, together with 2 ml. per patient of the oil-water emulsion. This mixture was then shaken up until a stable emulsion was obtained. This radioactive emulsion was added to about 80 grammes per patient of skimmed milk, and the whole was again emulsified in the mixer. Samples of about 80 grammes were checked for radioactive content with a scintillation counter, and any minor adjustments necessary were made to the contents in order to bring all the activities to the same value. A standard was prepared with the use of 20 μc. of KI^{131} in the same volume of water, and checked in a similar container to those used for the test meal. The reference standard was prepared from KI^{131} rather than the glyceryl trioleate, as the former is soluble in water and the problems of dilution and extraction of samples are considerably simplified. An aliquot of this standard was then used for comparison with blood samples from the patient.

The test meal was given for breakfast, together with 100 grammes of dietary fat. Blood samples were collected frequently during the first day and at shorter intervals during the next two days. Samples (12 ml.) were collected in oxalated bottles, and 10 ml. were pipetted into a standard jar for assay with a scintillation counter.

The patient's blood volume was taken as 7% of the body weight (Berlin *et alii*, 1957). The total circulating activity was then calculated by multiplication of the radioactivity per millilitre of blood by the blood volume. This was finally divided by the total radioactive dose administered, obtained from an assay of an aliquot of the KI^{131} standard. In this way the circulating radio-

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activity was expressed as a percentage of the administered dose.

The tests were always carried out under basal conditions on patients admitted to hospital. The results were plotted semi-logarithmically against time. From this plot the post-absorptive lipid clearance times to half intensity were read off.

Serum cholesterol concentrations were determined by the method of McIntyre and Ralston (1954). The range for normal subjects in our hospital is 150 to 250 mg. per 100 ml.

SUBJECTS

The test has so far been carried out on 40 patients with atherosclerosis and on 12 controls, as well as on patients with myxœdema and on some with essential hyperlipæmia without manifestation of atherosclerotic symptoms. The coronary atherosclerotic group included patients who had suffered recent myocardial infarction and a smaller group with angina pectoris due, on indisputable evidence, to atherosclerosis. These latter patients gave a classical picture of angina pectoris of effort, and their electrocardiograms showed ischæmic changes either at rest or after exercise. Their average age was 45·3 years (range, 25 to 72), an average weight of 143 lb. (range, 110 to 205) and an average serum cholesterol level of 308 mg. per 100 ml. (range, 175 to 600).

The controls consisted of a group of patients already in hospital for other reasons, who manifested no clinical evidence of coronary disease and had normal electrocardiograms. They were selected to be of similar weight and height to the coronary subjects investigated, and as far as possible a control and a patient were paired and investigated simultaneously. It was sometimes possible, by judicious selection, to have one control serve for two or three patients simultaneously. They had an average age of 40·2 years (range, 28 to 60), an average weight of 141·5 lb. (range, 92 to 217) and an average serum cholesterol level of 235 mg. per 100 ml. (range, 150 to 304).

RESULTS

The serum levels all rose rapidly in the first few hours to a maximum value of between 10% and 20% of the administered dose, after which the points fell away on a straight line when plotted semi-logarithmically (see Figure I). This is to be expected if absorption is completed in a few hours, and the material is then removed or metabolized at a rate depending on its serum concentration. Such curves have been noted many times previously with other biological tracers, such as I^{131} in thyroid investigations (Pochin, 1950).

In a series of 14 patients and six controls, the amount of labelled material excreted in the fæces was measured and found to be always less than 3%. Fæcal measurements were therefore discontinued, and it was assumed that in all cases virtually all the test meal was absorbed.

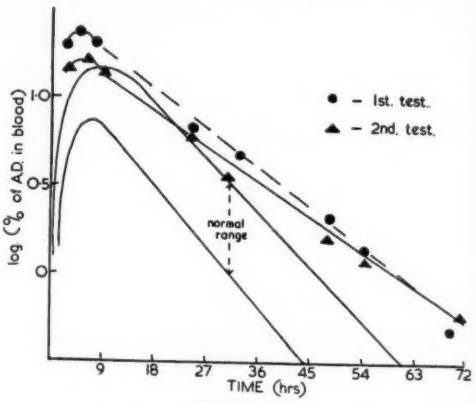

FIGURE I

A typical set of results of repeated tests on one subject

Consistency of Test

In a series of six subjects, the test was repeated a second time immediately after the serum level of radioactivity from the first test fell to a negligible level. Figure I shows a typical set of results obtained from a subject in this series. The results of the series are summarized in Table I. The reproducibility is seen to be satisfactory.

TABLE I

Results of a Series of Duplicated Tests

Subject	Time of Maximum Level (Hours)	Maximum Plasma Level (Percentage of Administered Dose)	Time for Half Clearance (Hours)
I			
First time ..	5	14·1	17
Second time ..	4½	9·1	16
II			
First time ..	6	10·2	8½
Second time ..	6	10·0	10½
III			
First time ..	5½	15·8	12½
Second time ..	4½	22·8	12½
IV			
First time ..	5	12	19½
Second time ..	4½	13·9	19½
V			
First time ..	5	18·8	12
Second time ..	6	13·3	12
VI			
First time ..	7	13·4	27
Second time ..	6	17·8	25½

Atherosclerosis

Figure II shows the results obtained on the atherosclerotic patients as compared with the normal controls. It is seen that in the atherosclerotic subjects the early serum levels rose to a

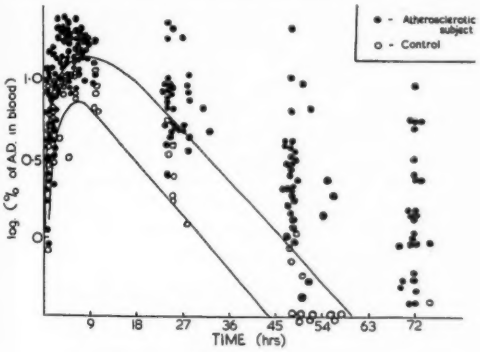

FIGURE II

Results obtained on 40 atherosclerotic subjects and 12 controls

higher peak than in the normal controls, but that there is considerable overlap between the two groups. This overlap becomes less marked as time proceeds, till there is almost a complete separation into two distinct groups towards 72 hours.

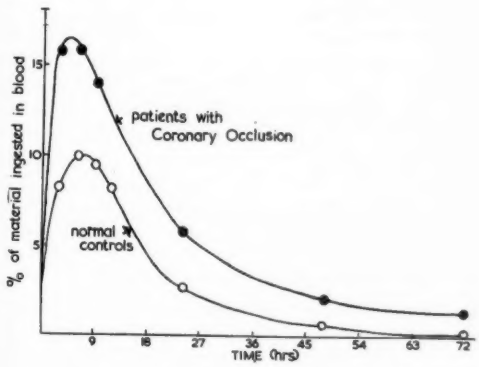

FIGURE III

Lipid tolerance curves for atherosclerotic subjects and controls (mean values)

In Figure III, the average results for each group are plotted on a linear scale. The average peak level of the atherosclerotic subjects is well above that of the normal controls, but the latter portions of these curves show an even more marked separation between the two groups. During the initial or absorption phase, the serum level in the atherosclerotic subjects is only about one and a half times that of the control group, whereas this ratio becomes a factor of three after 72 hours.

In each subject, the time taken for the serum level to fall to half its peak value was determined. This mean clearance time in the normal controls was found to be 9 hours, with a range of $7\frac{1}{2}$ to $10\frac{1}{2}$ hours. Figure IV is a scatter diagram

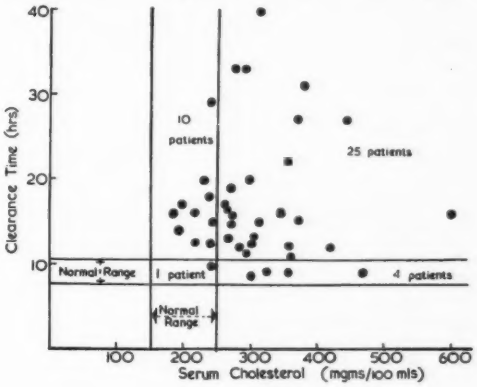

FIGURE IV

Lipid clearance and serum cholesterol values obtained in 40 atherosclerotic subjects

giving the clearance times and serum cholesterol levels in the 40 atherosclerotic subjects. The mean clearance time was 17 hours (range, 8 to 40 hours).

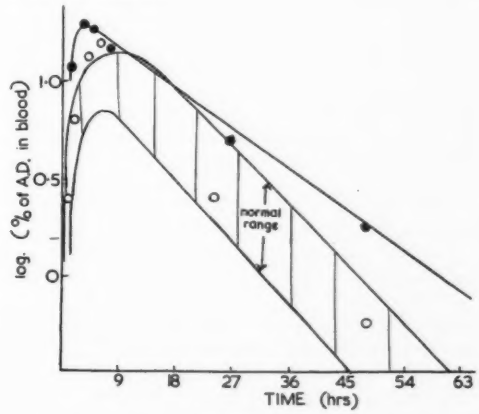

FIGURE V

The effect of exercise on the lipid tolerance curve in one subject

Effect of Exercise

Figure V shows the curve of an atherosclerotic subject taken under basal conditions, compared with the results for the same patient while

active as an out-patient. The considerable difference in the curves illustrates the importance of having measurements performed with the patient under basal conditions, because of the well-known effect of exercise on lipid metabolism.

Other Abnormal Groups

In the course of the investigation, we had the opportunity to obtain results on four other patients with disturbed lipid metabolism, but without symptoms of coronary atheroma. One was affected by hyperlipæmia with eruptive xanthoma, the remainder had myxœdema.

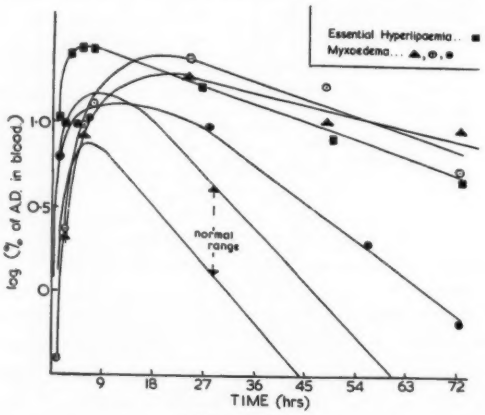

FIGURE VI

Results in one case of essential hyperlipæmia and three myxœdematous subjects

The results for this group are given in Figure VI, and are seen to be characterized by excessively high serum lipid levels and slow clearance times. For this group, the mean figures for serum cholesterol levels and clearance times are 346 mg. per 100 ml. and 27·5 hours.

Separation of Radioactivity into Protein-Bound and Free Iodide

It was recognized that some of the blood radioactivity would be in the form of free iodide, and some in the lipoprotein form. In the last 12 subjects studied, the free I^{131} in iodide form in the blood samples was extracted by means of exchange resins, and we were therefore able to determine separately the proportions of lipoprotein-bound and free radioactivity. The mean values of the lipoprotein-bound fraction for various groups are given in Table II. The validity of the resin extraction of the free iodide was checked by comparison with dialysis observations on some of the samples. In every case the dialysis result agreed with that obtained by resin extraction.

The scatter within the group was such that there is no significant difference between the results of the atherosclerotic group and normal controls, and up to the present not much significance has been attached to the results of this separation. It is of interest to note that the results in the group with essential hyperlipæmia do seem significantly higher than in the other two groups.

TABLE II

The Mean Values of the Fraction of Radioactivity in Lipoprotein-Bound Form, Expressed as a Percentage of the Administered Dose

Time (Hours)	Normal Controls	Atherosclerotic Subjects	Essential Hyperlipæmic
2	47	38	75
4	48·5	37	77
6	43	42	75
27	42	34	84
48	42	43·5	76
72	—	53	73

DISCUSSION

In many of the graphs presented above, we have indicated the normal range of values. This has been loosely taken as that range which includes the great majority of normal subjects regardless of other factors. The normal range defined in this manner is probably pessimistically large, and it is likely that the normal range is dependent on age, sex and many other factors. It is our intention to investigate further the influence of these factors. It is likely that when this is done the normal range for a given group will be narrower than that taken here, and that the deviation from normal of the abnormal patients will be even more pronounced.

Our interpretation of the curve for a given patient is that the initial rapid rise is an indication of the rate of absorption from the gastro-intestinal tract, while the steady decline in the semi-logarithmic plot is a measure of the rate of lipid metabolism.

The first part of the curve is similar to the well-established results of determinations of total serum lipids as reported, for example, by Barrit (1956). However, these biochemical investigations are essentially limited to a period of a few hours, and do not give any reliable indication of the rate of clearance beyond the point of maximum concentration in the curve. Also, the scatter in the biochemical results is such that there is considerable overlap between atherosclerotic subjects and normal controls. We find the same results in this part of our curves. We believe that the great advantage of the isotopic tracer technique is that the investigation can be continued for several days

without starving the subject. This enables us to separate out definitely the metabolic phase of the lipid tolerance curve, and gives us an index of the subject's rate of lipid metabolism—namely, the time of clearance to half value. Also, as is seen in Figure II, owing to the reduced rate of lipid metabolism in the atherosclerotic group, the overlap between the points becomes less as time proceeds and ends in an almost complete separation between 48 and 72 hours.

Of course, one always has the difficulty that some degree of atheroma may exist in patients chosen for controls, which has so far not declared itself in overt symptoms. Indeed, in one of our control patients, the points are seen to lie outside the normal range. This may indicate an early manifestation of atheroma, and this patient will be checked at later times for other signs of disease.

Referring to the scatter-diagram connecting lipid clearance times with serum cholesterol values in atherosclerotic subjects, we see that both parameters were outside the normal range in 25 cases, that clearance times alone were raised in 10 cases and cholesterol values alone in four cases, while in one case only were both values inside the normal range. It would thus appear that the abnormalities in lipid clearance times correlate better with atherosclerosis than do raised cholesterol values, and that if both parameters together are required to lie in the normal range in order to indicate absence of atherosclerosis, an erroneous conclusion would have been drawn only once in 40 cases. This suggests that the results of the lipid tolerance tests, taken together with the serum cholesterol values, may well lead to a more accurate delineation of the disease. The exceptional case is of interest.

The patient was a young man, aged 34 years, who had suffered a myocardial infarct two years previously. Since that time he has maintained himself on a diet of low fat content. His resting electrocardiogram was normal, but after exercise there was definite lowering of the *S-T* segment with inversion of *T* waves.

This suggests that a diet of low fat content may be influential in bringing the abnormal cases closer to the normal range.

The other factors noted in the course of this investigation—namely, the effect of exercise in lowering the points and the slower lipid metabolism in myxœdematous patients and those with essential lipæmia—are in line with the accepted concepts in this field. Thannhauser and Stanley (1949) suggest that the I^{131} glyceryl trioleate is a satisfactory tracer of disordered lipid metabolism.

On the completion of this investigation, our attention was drawn to the work of Likoff *et alii* (1958), who have used a similar method to investigate the lipid metabolism in similar groups of patients. The only difference in our techniques consists in our continuing the curve for three days, whereas they terminated theirs at 24 hours. The results up to 24 hours are in agreement.

ACKNOWLEDGEMENTS

We are grateful to the physicians at St. Vincent's Hospital for allowing us to investigate patients under their care, and to the Commonwealth X-ray and Radium Laboratory for supplying the isotopically labelled lipids. The work has been considerably helped in its various stages by the resident medical officers and registrars attached to the Unit of Clinical Investigation. Also, we should like to thank the sponsors of the Hungarian Fellowship in Nuclear Medicine for appointing Dr. G. S. Farkas to the Fellowship, which greatly facilitated the investigation in later phases. We should like to thank Mr. F. A. Rocke for many discussions in the early part of the work. The investigation was supported by a grant from the Atomic Energy Commission, to whom we should like to express our thanks.

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A Review Written by Request

CORONARY ARTERY DISEASE[1]

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THE clinical prominence of coronary disease is due to the economics of heart dysfunction, the dramatic impact of acute cardiac disorders, and the tragedy of sudden death; this so distorts the outlook that the place of coronary disease as merely a part of general vascular disease is often overlooked. At the same time the generalized disease is notoriously patchy, so that emphasis on symptoms related to heart or central nervous system may depend on sites of maximal incidence as well as on the characters of tissues affected.

The complexities of muscle physiology and vascular pathology have retarded progress, and premature attempts to hasten clinical interpretations have produced many unattested hypotheses; the *post hoc ergo propter hoc* argument (so apparently rational, so often fallacious) has been frequently invoked. Furthermore, the burgeoning literature (born partly of attempts to derive far-reaching conclusions from slight premises) is now too voluminous to be covered concisely; thus, although an attempt has been made to include significant contributions, it is appreciated that important papers have been omitted.

This review is considered in three parts: I, changes in coronary arteries; II, occlusion resulting from these; III, consequential changes in heart muscle.

PART I: CORONARY DISEASE

Although much of our knowledge comes from direct observation of coronary vessels, important information is derived from studies of vascular disease elsewhere and of general metabolic phenomena. In the space available these can only be mentioned briefly.

GENERAL VASCULAR DISEASE

There has been confusion here, due to lack of agreement over terms. Two main conditions have been recognized: (i) a patchy softening in the intima of larger vessels described as atheroma; (ii) a generalized thickening and hardening of the smaller arteries and arterioles referred to as arteriosclerosis. Each term has, in turn, been applied generically to all types of generalized non-specific disease. In view of the difference in physical character of the two processes, as well as the meaning of the terms, this has indicated a curious lack of appreciation of the structural changes involved. Marchand, in 1904, discussing the recognized frequent association of these two conditions, suggested the term "atherosclerosis".

This essentially natural and simple notion, which had been accepted increasingly, was ignored by the Congress of the International Society of Geographical Pathology in 1934, at which the generic term "arteriosclerosis" was adopted. Although it gained some acceptance, this was not general; the most recent attempt to standardize the nomenclature has been made by a WHO study group (1958), at which the term "atherosclerosis" has been accepted and "arteriosclerosis" discarded.

The recognition of both types of change—the patchy swelling of the subintima and the thickening of the whole wall, together with the frequent association of these two processes in one vessel—is essential to the understanding of vascular disease in general and of coronary disease in particular.

PATHOLOGY OF CORONARY DISEASE

Any diseases affecting blood vessels may be found; but arteritis, polyarteritis, Buerger's disease, etc., are not discussed here. Non-specific arterial disease, though commonly considered to be separate, is part of a general atherosclerosis.

True arteriosclerosis or arteriolosclerosis is diffuse, affects small arteries and arterioles, and is responsible for general muscle insufficiency giving anginal pain; fibrosis occurs diffusely with, at first, hypertrophy and later atrophy of muscle. It is often associated with atherosclerotic lesions.

[1] Received on March 4, 1959.
[2] Professor of Pathology.

In atherosclerosis, an extensive range of complex changes is difficult to place in satisfactory chronological order, because various processes are proceeding simultaneously and in different combinations. They may be described, without prejudice, in order of size and degree of change. A statement regarding these is desirable, since lack of knowledge of structural changes appears to be the basis of many infelicitous statements in the literature.

The most obvious changes occur in the intima. Early simple thickening and fibrosis, with gradations from normal to obviously pathological states, were regarded as abnormal by Jores (1904), but as due to aging by Aschoff (1907). In the mildest cases, a swelling of ground substance and collagenous fibres occurs; sometimes cholesterol crystals and calcification are seen in even small lesions.

Lipid accumulation occurs in either the superficial or deep layers of the intima. When it is superficial, collections of phagocytic cells lie immediately below the intima. In deeper accumulations, numerous phagocytes may be associated with or independent of superficial collections. Fibrosis is sometimes prominent and phagocytes are often absent, but fat and cholesterol or liquefaction spaces occur. This fatty material either comes from degeneration of local tissue cells or blood, or is deposited from the serum. Fibrin is often demonstrable, having been deposited on the surface and incorporated in the wall, or having been deposited in the wall after seepage of plasma elements from the lumen, or it may be part of an intramural hæmorrhage. The intima gradually becomes grossly thickened.

Hæmorrhage occurs in the wall at various stages. This may be intimal or in other layers. Recognizable clot gradually degenerates to an amorphous mass, which rapidly loses its hæmoglobin and is organized by granulation tissue.

Increased cellularity occurs, and capillary vessels communicate with both vasa vasorum and lumen. These gradually become larger and develop into arterioles or venules. They recanalize the region (Snow, Jones and Daber, 1955), and are large enough in some cases to be significantly functional.

In larger lesions the tissue is often arranged in distinct layers, indicating that the processes have been episodic (Morgan, 1956). Elastic tissue may occur in multiple layers and round small intraintimal vessels. Smooth muscle is present, especially round capillary vessels.

Calcification occurs in various forms, distribution and amounts, independently of the size of the lesions. A thrombus may be attached to one wall without completely obstructing the lumen; an endothelial covering develops early, cells and hæmoglobin disappear, and organization occurs. The atheromatous mass may rupture into the lumen, and either cholesterol crystals (Zak and Elias, 1949) or the plaque may cause coronary embolism.

The media undergoes atrophy beneath the thickened intima, and vasa vasorum become prominent, often communicating with vessels of the plaque. The adventitia shows increased vascularity and sometimes perivascular small round-cell accumulations.

PATHOGENESIS

The processes fall into two groups: (*a*) deposition of lipids (especially cholesterol) in the wall associated with alteration in serum lipids—this has been regarded as either a physico-chemical or a cellular phenomenon; (*b*) deposition of fibrin on the intima.

Cholesterol Deposition

Cholesterol in the vessel wall has been known for over 100 years (Virchow, 1856), and the high content of cholesterol esters and various lipids in atheromatous lesions has often been demonstrated (Windaus, 1910; Leary, 1935*b*, 1949; Hirsch and Weinhouse, 1943; Morrison and Johnson, 1950). Numerous ethnological, morphological, experimental and biochemical studies provide a literature too great to be covered here; an excellent review is given by Katz and Stamler (1953). Two factors require consideration: precipitation of cholesterol from the plasma and changes in the wall facilitating this deposition.

Serum Lipids.—Attention was first directed to cholesterol by Anitschkow's (1913) experimental studies. Much investigation followed and conflicting results were obtained, but gradually a relation between hypercholesterolæmia and atherosclerosis was established (Mjassnikow, 1925; Davis, Stern and Lesnick, 1937; Morrison, Hall and Chaney, 1948; Frantz, 1955). The importance of hypercholesterolæmia of diabetes was shown by White (1934). Some experimental discrepancies were due to different states of the lipid; in colloidal form cholesterol produced lesions much more rapidly and more like those of man (Pollak, 1953).

Lipid particles, known as chylomicrons, which appear in the plasma after meals, are not significantly different in normal and atherosclerotic individuals (Zinn and Griffith, 1950), but they remain for a longer period with increasing age (Becker, Meyer and Necheles, 1949). They are more numerous in hyper-

cholesterolæmia (Moreton, 1947). It is possible to follow the transport of fats using isotope-labelled material (Gould, 1951; Likoff *et alii*, 1958).

The various serum components, which can be separated by ultracentrifugation, fractionation and electrophoresis, are aggregated in a sterol-lecithin-protein combination. It appears that the beta-lipoprotein is the important carrier of cholesterol; thus the S_f 10/100 lipoproteins, beta-lipoproteins and cholesterol are closely related (Gutman, 1953). Attention has been paid to cholesterol-phosphospholipid ratios, but these give inadequate information. Although the lipoprotein component is raised in atherosclerosis (Gertler, Garn and Lerman, 1950; Oliver and Boyd, 1953), it is even more significant that where the alpha-lipoprotein is diminished, the beta-lipoprotein level is raised (Russ, Eder and Barr, 1951; Barr, Russ and Eder, 1951); the important feature, therefore, is the alpha-beta ratio (Nikkalä, 1953; Kunkel and Slater, 1952; Swahn, 1953). The serum beta-lipoprotein level increases with ingestion of food and then gradually diminishes; but this occurs more slowly, and the general level is greater in males, with advancing age (Tamplin *et alii*, 1954) and in some " metabolic " diseases such as diabetes, nephrosis and myxœdema.

Considerable attention has been drawn recently to these lipid-protein complexes in the use of the term macromolecules. Hueper (1942), employing the macromolecular polymers that were then in use as " plasma expanders ", found that he produced lesions resembling atheroma. Macromolecules of lipoprotein are prominent in atherosclerosis (Gofman *et alii*, 1950*a*, 1950*b*, 1952; Jones *et alii*, 1951; Lyon *et alii*, 1952). Present studies are rapidly unveiling vistas of fascinating complexity as indicated by recent work on the influence of magnesium in the diet (Gottlieb *et alii*, 1959).

To summarize: there is a balance between lipids in the serum and the tissues. Normally, lipoprotein is depolymerized and hydrolysed; if this process is delayed, the natural excess will result in a surplus of cholesterol, since a high serum beta-lipoprotein level will maintain dispersion of cholesterol. When more is available in the serum, this will diffuse into the wall in larger amount. Excess of beta-lipoprotein is probably due to some defect in the processes normally controlling it.

At the same time, the localization of atherosclerotic lesions shows that local factors must also be significant.

Condition of the Vessel Wall.—In most studies, attention is directed entirely to humoral aspects of the problem. However, not only do some vessels and parts of vessels differ from others, but cholesterol deposition may not necessarily be the first change; ground substance changes have long been recognized. The distribution of lesions, commonly occurring in the male coronary artery and the lower part of the abdominal aorta, has emphasized the normal thickening here (Dock, 1946, 1951). Whether the intima is different or just more voluminous is not certain.

Peculiarities of ground substance have been emphasized by Faber (1949). Pollack (1949) considered that the endothelial cells were actively phagocytic for lipid, and that this fact determined the accumulation of this material.

Observations of vessel walls show that, amongst other features, cholesterol synthesis occurs (even though at less than one-quarter the rate in the liver), carbonic anhydrase is present, and thyroid secretion stimulates oxygen consumption (Page, 1954). The importance of changes due to aging or other processes had been emphasized by Duff (1935) and by Lansing, Alex and Rosenthal (1950); vascularity of the wall was discussed by Winternitz, Thomas and Le Compte (1938), and the significance of anoxia by Hueper (1944, 1945).

No clear picture has emerged, but the important lines of attack appear to be on the ground substance, particularly in view of the polymucopolysaccharides in the serum (Schwarz and Gilmore, 1958), and on enzyme activity in the wall.

Cellular Lipophage Accumulation

This hypothesis, based on experimental atherosclerosis in rabbits, proposes that cholesterol is conveyed by lipophages into the intima (Leary, 1935*a*). In 1941, Leary suggested that these cells came from the reticulo-endothelial system at a distance; details need not be discussed here.

Differences at different ages explain cholesterol being metabolized and the intima becoming fibrosed (by " fibrolipophages ") in the young, whereas later degenerative changes occur; but this does not adequately explain deeply-seated fatty collections (Morgan, 1956), and Horn and Finkelstein (1940) could not correlate age with degeneration of intimal plaques. The lipophage thesis has been supported by Gordon (1947); the observations can be confirmed (Rannie and Duguid, 1953), but mitotic figures in some cells indicate their local origin (McMillan and Duff, (1948). It should be appreciated that one explanation does not necessarily exclude others, and, just as elsewhere, material

may either be moved physico-chemically or carried by cells; so probably lipid transport by cells may well be part (even though small) of the phenomenon.

Intimal Thrombosis

Although plaque formation from thrombi was proposed by Rokitansky, objections of Virchow caused it to be forgotten for a century. A relation of mural thrombi to atheroma was noted by Horn and Finkelstein (1940) and by Paterson (1941), but its significance was unrecognized until the reintroduction of the thrombotic hypothesis by Duguid (1946). Though this attracted little attention at first, corroborative evidence in the form of demonstrable organization of thrombi, the localization of lesions and intimal lamination soon appeared. Duguid (1948, 1949) elaborated it further, and was supported by Geiringer (1951), by Crawford and Levene (1952) and by the experimental work of Harrison (1948) and Heard (1952), in which injected fibrin, attached to vessel walls, developed an endothelial covering and basal organization.

The observations on the relation of serum lipids to coagulation were now applied, and general support for the importance of mural was thrombi obtained. Further experimental data were provided (McLetchie, 1952) by thrombus production following injections of rabbits with Russell viper venom, and by lesions simulating human atherosclerosis.

Effects of Heparin.—Heparin was used clinically first to minimize thrombosis, and the early results were favourable in atherosclerosis (Engelberg, 1952; Engelberg, Kuhn and Steinman, 1956). However, it altered blood lipid content (Hahn, 1943) by the production of a clearing factor (Anfinsen *et alii*, 1952). Heparin is formed by mast cells, and normal blood heparinoids are diminished in atherosclerosis (Nikkalä and Majanen, 1952).

The clearing factor, an enzyme, a lipoprotein lipase (Anfinsen, 1955) which catalyses hydrolysis of the trigylcerides of chylomicrons, is present in normal serum (Engelberg, 1956); its amount is reduced in atherosclerosis (Oliver and Boyd, 1953; Herzstein *et alii*, 1954). The freed fatty acids are bound by albumin.

Protamine, an anti-heparin agent, reverses the clearing effect, increasing the "low density" lipoproteins. Naturally-occurring clearing factor inhibitor (probably a glycoprotein) has been demonstrated; this increases with age (Day and Wilkinson, 1958); this may partly explain the increase in atherosclerosis with age (Angervall and Hood, 1957). That other factors may be active is shown by the effect of anti-oxidants such as cysteine on polymerization of lipoproteins (Harman, 1958).

Thus, though the results of heparin therapy are disappointing, its study has shown one lipid-control mechanism (by way of mast cell activity); it influences clotting, incidentally. The application to treatment has been premature; poor results are understandable if heparin produces a long-range (lipid) rather than an immediate (anticoagulant) effect. The therapeutic use of anticoagulants has been strongly criticized (Evans, 1954), but the results of dicoumarol therapy have been assessed and cautiously approved (Engelberg, Kuhn and Steinman, 1956; Keyes *et alii*, 1956; Honey and Truelove, 1957; Bjerkelund, 1957).

Coagulability of the Blood.—Many features of thrombosis are still obscure. First, it is not a matter of simple clotting, but a complex involving platelet deposition. Apart from the mechanical influences in turbulence of the stream or stasis, increase in platelets and changes in electrolytes and carbon dioxide content, which cause alterations in their electrical charge, are important but subtle factors. These need more attention in atherosclerosis.

The numerous factors in coagulation need not be discussed, but changes such as low antithrombin titre (Pomeranz *et alii*, 1953) and increased fibrinogen have been described in coronary disease.

It has been long known that there is increased coagulability after meals (Mills, 1923), and that fats (McFarlane *et alii*, 1941; Waldron *et alii*, 1951) and more specifically lipoproteins (Fullerton *et alii*, 1953; Fullerton, 1955) facilitate coagulation. The question has been reviewed by O'Brien (1957); but clotting is not synonymous with thrombosis, so that the immediate application of these observations is uncertain (Poole, 1958).

Fibrinolysin may influence removal of smaller thrombi of the type seen in coronary vessels. Recent in-vitro tests, using Russell viper venom, show that beta-lipoproteins inhibit fibrolysin activity (Greig and Runde, 1957; Merigan *et alii*, 1958; Maclagen *et alii*, 1958). These and other observations have still to be correlated. Cold precipitable substances (cryoglobulins) in atherosclerotic disease (James and Drake, 1953) have been noted. Mucoproteins and hexosamines in the plasma (Schwarz and Gilmore, 1958) may be associated with depolymerization of connective tissue mucopolysaccharides, and draw attention again to tissue plasma interrelations.

To summarize, it is commonly implied that lipid deposition and intimal thrombosis are mutually exclusive alternatives. Since serum lipid levels (and the type of fat) are closely related to coagulability of the blood (which is an adjunct of platelet deposition), we have an example of misleadingly restricted viewpoints becoming gradually embodied into a satisfyingly composite design.

ÆTIOLOGY

Various general factors have been thought significant, but when basic principles are considered, most of them are too vague to have a precise significance ; they are discussed briefly.

Heredity

A familial incidence has been noted (Cassidy, 1946), and is more apparent in younger individuals (Yater *et alii*, 1948) ; a good review is given by Thomas and Cohen (1955). Since responses of tissues depend on their biological make-up, some genetic influence, as in diabetes, is to be expected, and the hereditary factor in familial xanthomatosis (Muller, 1939 ; Aldersberg, Parets and Boas, 1949) is a good example.

Age

Atherosclerosis is found in older individuals (Cassidy, 1946 ; Lansing, Alex and Rosenthal, 1950 ; Adams, 1953 ; Levy, 1953 ; Spain *et alii*, 1954 ; Peel, 1955) ; the changes begin shortly after birth (Dock, 1946) and progress during life (Gross *et alii*, 1934). When lesions are graded in severity, there is a rapid increase during the 30 to 49 years period (White *et alii*, 1950).

The underlying changes in aging are extremely complex and cannot be dealt with here. The ductless glands play a part, and when vascular changes occur and these produce further alterations in various tissues, including those which themselves (like the ductless glands) control bodily activities, a vicious circle is set up.

The end result of such factors would be expected to be variable, and, indeed, atherosclerosis may be no more serious in extreme age than in younger people (Russell, 1952). Though atherosclerosis increases with age, the degree of occlusion is not obviously related to age *per se* (Morgan, 1956).

The incidence of vascular disease conforms with observations on changes in lipids with increasing age. Alterations in macromolecules, serum levels of lipoprotein and cholesterol, and clearing of lipoproteins are fundamental features which may determine the ætiological importance of age in atherosclerosis.

Race

Differences in incidence of atherosclerosis in various races are observed, but these become insignificant when the comparison is restricted to individuals of similar social status, dietetic habits, and the like (Hunter, 1946).

Sex

The more frequent occurrence of atherosclerosis in males (Levine and Brown, 1929 ; Ackerman *et alii*, 1950 ; Firstbrook, 1951) has been found particularly in the later years (Ryle and Russell, 1949 ; White *et alii*, 1950 ; Master *et alii*, 1956). The greater thickening of the intima of the male coronary artery has been noted (Dock, 1946), and the higher serum lipoprotein level in males may be significant (Eder, 1955).

Endocrines

Attention has been directed to the gonads and thyroid gland.

From clinical observations, male hormone should produce or aggravate and œstrogens inhibit or diminish vascular changes ; however, the matter is confused. Androgens administered to eunuchoid males lower serum alpha-lipoprotein levels (Furman *et alii*, 1954), and there is increased atherosclerosis in females after bilateral oophorectomy (Rivin and Dimitroff, 1954). On the other hand, castration accelerates atherosclerosis in cholesterol-fed rabbits (Shapiro, 1927). When œstrogens are given, atherosclerosis is diminished in males (Rivin and Dimitroff, 1954), and lipoprotein levels rise in post-menopausal females. In cockerels, however, œstrogens produce different effects in the aorta and coronary vessels (Katz, 1952). Thus the results in man follow expected lines, but animal experiments require further elucidation.

The place of the thyroid gland in experimental work is clearer. In hypothyroidism after thyroidectomy, acceleration of atherosclerosis occurs in rabbits (Shapiro, 1927) ; a review is given by Black and Campmeier (1934). Coronary atherosclerosis in dogs follows thiouracil feeding (Steiner, Kendall and Bevans, 1949). Other ductless glands require further study.

Hypertension

Hypertension is frequently found associated with atherosclerosis, and in a large proportion of patients with coronary occlusion (Master, Dack and Jaffe, 1939*b*). Coronary atherosclerosis is more prominent in hearts of hypertensives (Lober, 1953), and hypertension accelerates and aggravates cholesterol-induced disease (Dill and Isenhour, 1942). When the influence of

serum lipoprotein is being assessed statistically, a better correlation is obtained if diastolic blood pressure is included as a factor (Gofman *et alii*, 1954). However, there is not a direct correlation between the extent of coronary occlusion and hypertension (Morgan, 1956); furthermore, no suggestion of the possible mode of action of raised blood pressure has yet been proposed.

Diet

After it had been demonstrated that some foods produced intimal change, Stukkey (1911) and Wesselkin (1913) showed that these contained cholesterol, and Anitschkow (1913) and Wacker and Hueck (1913) produced intimal changes in rabbits. Numerous experimental and clinical observations followed.

The significance of diet was inferred from the diminution of atheroma in starving wasted people in both World War I (Aschoff, 1924) and World War II (Malmros, 1950; Pihl, 1952; Strom and Jensen, 1951); also, individuals with wasting diseases showed less arterial change than others (Wilens, 1947*b*). People on a vegetarian diet showed minimal vascular change (Steiner, 1946), and racial differences appeared to be related to eating habits (Bronte-Stewart *et alii*, 1955). The question has been reviewed by Hirsch and Weinhouse (1943).

Experimental work on special components indicates the possible significance of pyrixodine, ascorbic acid, choline and amino acid deficiencies. The special experimental features, however, suggest that these are not directly applicable to the problem (Keys and Anderson, 1954). A review of experimental work was given by Katz and Stamler (1953).

Sinclair (1956) regards the essential fatty acids as important in allowing deposition of cholesterol, but this is not generally accepted (Keys *et alii*, 1957; James and Lovelock, 1958). The importance of unsaturated fats in depressing the serum cholesterol level has been emphasized (Bronte-Stewart *et alii*, 1956), and some vegetable and marine animal oils are important; attention has been paid to sunflower seed oil (Gordon *et alii*, 1957). In addition to the in-vivo experiments, studies have been made of excised arteries (Wilens, 1951), and the uptake of cholesterol by aortic endothelial cells grown in tissue culture has been found to be inhibited by unsaturated fatty acids (Rutstein *et alii*, 1958). To what extent these findings are generally applicable is uncertain.

An outstanding feature is the discrepancy between different investigators; but some general conclusions have been put forward by Keys and Anderson (1954). Dietary cholesterol has little or no influence on blood cholesterol level in ordinary diets (Mellinkoff *et alii*, 1950; Wilkinson *et alii*, 1950), and there is no evidence that dietetic cholesterol influences atherosclerosis in man (Pihl, 1952; Gutman, 1953; Keys, 1954). The effect of excessive caloric intake, *per se*, is small (Weiss and Minot, 1933). The total fat content of the diet does not have a great effect in adults; but the type of fat (for example, animal fats and lipoproteins) does.

The important factors are clearly those which control the serum lipids, since these are not necessarily to be correlated directly with diet. More information is required. The evidence for the importance of fats is purely circumstantial; there are more assumptions than facts; but dietary fat intake is susceptible of measurement and control (Bronte-Stewart, 1958) and is therefore a challenge to both laboratory and clinical workers.

Obesity

The importance of overweight has been emphasized (French and Dock, 1944; Wilens, 1947*a*; Master, Jaffe and Chesky, 1953). The general attitude in insurance policies is well known; it was stated by Dublin in 1930. The significance of figures given is doubted by Keys (1954), and others (Yater *et alii*, 1948; Faber and Lund, 1949; Keys and Anderson, 1954) also maintain that there is as yet no proof that obesity, *per se*, is specially important.

The matter is complex, and difficulties and apparent contradictions are due to attempts to obtain over-simplified answers to problems. The undoubted improvement of patients with coronary occlusion following dietetic restrictions may be due to diminution of gastro-cardiac reflexes and lowering of metabolic rate and thus of cardiac output (Master, 1936). Such factors may be much more important than diminution of weight.

Diabetes

Atherosclerosis occurs relatively frequently at a younger age and in a more severe form in diabetics (Rabinowitch, 1935); fatal coronary disease is twice as frequent (Blotner, 1930; Enklewitz, 1934; Fitz and Murphy, 1924; Nathanson, 1932; Clawsen and Bell, 1949). That insulin-resistant diabetics show more gross atherosclerosis at an earlier age (Downie and Martin, 1959) suggests again that the problem is more complex than is generally realized.

The special association of coronary disease with cholelithiasis (Boyd-Campbell, 1936; Miller, 1932) is also circumstantial evidence of a metabolic factor involving lipid changes.

Habits

Different conclusions have been reached, but it is now generally conceded that smoking increases the incidence of complications of atherosclerosis, there being a statistical difference between smokers and non-smokers (Hammond and Horn, 1954; Doll and Hill, 1954).

On the other hand, alcohol does not appear to have a significant direct effect (Wilens, 1947*c*).

Occupation

The early interest here, possibly because of the high incidence in medical men (Curtin, 1897), is still maintained (Conybeare, 1952). The disease, as indicated by occlusion, is known to be commoner in the "better" social groups (Osler, 1910; Logan, 1952). Numerous studies have shown that, in general, sedentary workers are more frequently affected than manual workers (Ryle and Russell, 1949; Master, Dack and Jaffe, 1941; Master and Jaffe, 1952; Morris *et alii*, 1953) In order to exclude possible complicating factors, comparisons were made of presumably comparable workers showing different degrees of activity, such as bus drivers and bus conductors and postal clerks and postmen; the more active individuals showed less occlusions (Benton and Rusk, 1954). There seems little doubt that physical activity is a protection, rather than the reverse, against coronary occlusion (Morris and Crawford, 1958).

Psychical Stress

Although the evolution and precipitation of coronary occlusion may be correlated clinically with emotional factors, especially executive responsibility (Bronte-Stewart *et alii*, 1955; Ryle and Russell, 1949; *inter alios*), the multiplicity of variables prevents clear-cut demonstration of a direct relation. Modern interest is in the hypothalamic-hypophyseal-adrenal chain in psychosomatic phenomena, and emotional stresses have been shown to influence blood coagulation and, both quantitatively and qualitatively, serum lipids, to modify the hæmodynamic state and probably, from comparison with other tissues, to affect the vascular intima. Their persistent action for long periods will produce significant effect. At the same time, this involves a complex interrelation of many agents, some of which at present are obscure. Thus, though emotional factors are obviously important, their precise significance and mode of action, especially in any given case, are still intangible, and without more precise information must be grouped with the vague general influences. The directions for research, however, are becoming clearer.

SUMMARY

Atherosclerosis is a general vascular disease due to abnormal lipid metabolism, effects of which are becoming recognized, but its basic nature is still unknown. Organization of, and reactive changes in, lipid deposits and mural thrombi (which are related phenomena) produce the lesions. General ætiological factors are related to these. Peculiarities of arterial walls, which are probably significant, still await demonstration.

PART II: CORONARY OCCLUSION

Diminution of coronary blood flow occurs from reduction of the arterial lumen ranging from partial to complete closure; sometimes it happens with normal vessels. Consequently various names have been applied, depending on the circumstances.

TERMINOLOGY

From the structural viewpoint, the terms coronary sclerosis and atherosclerosis have been used to imply the complication of obstruction. This usage depended on the stage of evolution of ideas (and fashions in terminology) in general vascular disease, and on whether degenerative or hyperplastic changes predominated.

Physical obstruction has been designated thrombosis or occlusion. The former, whether complete or incomplete, was used almost exclusively at one time, until thrombosis was found to be less common than at first thought. The term "occlusion" was then suggested (De Coursey, 1934) as being non-committal and more accurate; this has been commonly applied for about two decades. The term "myocardial infarct" is sometimes used indiscriminately for occlusion.

More recently, the observation that disturbances of blood supply may occur in the absence of gross structural changes has modified the position. The term "coronary insufficiency", first used 25 years ago (Dietrich and Schwiegk, 1933; Büchner, Weber and Haager, 1935; Levey and Bruenn, 1936; Uhlenbruch, 1938) emphasizes the discrepancy between blood supply and tissue demand (Horn *et alii*, 1950; Master *et alii*, 1956). A great demand may occur with physical effort, emotion, over-eating, fever and tachycardia. Psychical factors are often more important than physical ones; those which cause continued rather than temporary discrepancies, such as diminution of blood supply as in shock and hæmorrhage and anoxia, are specially significant.

"Coronary insufficiency" and other terms such as "coronary failure" (Blumgart,

Schlesinger and Zoll, 1941) and "intermediate coronary syndrome" (Graybiel, 1955), which emphasizes the relation to both angina pectoris and cardiac infarction, all indicate a functional state, but should be used in conjunction with, and not as alternatives to, morphological terms.

INCIDENCE

Vascular occlusion, which attracts attention to the presence of arterial change, is naturally intimately related to the disease itself. Atherosclerosis is notoriously patchy in distribution, but whether or not mechanical as well as metabolic factors play a part, coronary vessels are commonly affected. The greater intimal thickening in males at birth (Dock, 1946) may be important.

Coronary atherosclerosis constitutes as much as 30% of organic heart disease (Munck, 1946). Coronary occlusion is said to cause from 65% (Hamman, 1941) to 80% (Cassidy, 1946) of cardiac deaths.

Gross atherosclerosis has always occurred, having been found in Egyptian mummies (Shattock, 1909; Ruffer, 1911); however, increase has been claimed in recent times (Logan, 1952; Davidson, 1953). It is said to be influenced by fashions in diagnosis and (in the older age groups) by an aging population (Master, 1947). When we consider that it is commonplace nowadays for lay people to "diagnose" coronary disease in individuals who die suddenly or have chest pain, whereas 30 years ago coronary occlusion was a rare medical event, it is difficult to escape the conclusion that much of the modern increase in coronary disease is artificial. At the same time, when allowances are made for the increased expectancy of life and other factors, there seems to be a definite increase (Ryle and Russell, 1949; Morris, 1951). Furthermore, there appears to be an undoubted increase in younger individuals (Yater *et alii*, 1948; Grorud, 1950; Gertler, Garn and White, 1951; Enos, Beyer and Holmes, 1955).

Associated Lesions

Occlusion may produce different and sometimes more extravagant effects when the vessels are atypical in distribution. Origin of both the coronary vessels from the pulmonary truncus is incompatible with life, so that an anomalous origin of one might be expected to shorten life; however, such a condition was found in a man at 90 years (Cronk, Sinclair and Rigdon, 1951). Absence of the left coronary artery has been observed in cases of infarction (Roberts and Loube, 1947), but should be regarded only as an incidental finding, since individuals with this anomaly have lived to old age (King, 1941).

Various conditions, such as polyarteritis nodosa, thrombo-angiitis obliterans (Saphir, 1936) and various aneurysms, may cause closure of the arteries, but do not require a special statement here.

Site

Many studies have been made of the coronary circulation and its usual distribution (Spalteholtz, 1907; Gross, 1921) and variations (Schlesinger, 1940; Blumgart, Schlesinger and Davis, 1940; Wessler, Zoll and Schlesinger, 1952). Atheromatous change and occlusion occur most frequently in the anterior descending branch of the left artery (Saphir *et alii*, 1935; Applebaum and Nicolson, 1935; Munck, 1946; Wartman and Hellerstein, 1948; Yater *et alii*, 1948), but both right and left arteries may be involved (Horn and Finkelstein, 1940; Schlesinger and Zoll, 1941; Snow *et alii*, 1955). Although there may be one obstructive lesion, lesions are often multiple. Obstruction occurs particularly near the origin of the vessels. Various lengths of the artery may be affected, but often this is short—about 5 mm. (Schlesinger and Zoll, 1941).

Frequency of Gross Obstruction

This is commonly expected to be due to a thrombus, but such an obvious and dramatic cause may not be demonstrable. Obstruction by thickening of the wall is usually present, but sometimes this is absent; frequently there is gross obstruction to a vessel without demonstrable change in the myocardium. These discrepancies demand close attention.

PATHOLOGY

The narrowing of the lumen occurs in several ways and at different rates. Whether a significant alteration in the blood flow to an area develops depends on several factors. First, change must occur at a definite speed, since stimuli depend on rate of differences; for example, if the blood supply is diminished slowly, the affected tissue may accommodate itself in an astonishing manner. Secondly, collateral circulation develops, often to a remarkable degree. Redistribution of cellular function and compensatory hypertrophy of areas not affected may take place. On the other hand, with rapid or sudden change maximal disturbance occurs.

Gradual Occlusion

Obstruction to the vessel is due to exaggeration of the atherosclerotic processes and, indeed, results from their natural progression. The

effect on the lumen ranges from slight diminution to complete disappearance. Gross narrowing may extend for some distance along the vessel, but is often localized to small areas.

The shape of the lumen, on cross section, may be round or oval (the occlusion developing concentrically) or irregular and eccentric (due to plaque formation on one part of the wall). The wall may be uniform, or may show localized lesions of lipid deposition, collections of fat crystals or liquefaction with irregular fibrosis; the intima often shows, particularly in localized areas, typical lamination.

Thrombi occur in mural or occlusive forms. These are discussed later, but are important because they may merge into intimal plaques, and they occur without gross myocardial disturbance (Nathanson, 1932; Appelbaum and Nicolson, 1935; Munck, 1946; Karsner, 1955). Hæmorrhage occurs both beneath the intima and in other parts of the wall; subintimal hæmorrhage may produce a projection into the lumen. Organization of thrombi and hæmorrhagic zones is often prominent, and sometimes the capillary vessels, which become large, may play a part in developing a collateral circulation. Calcification, slight or extensive, may be found anywhere from the superficial part of the intima to the adventitia.

The blood flow through a partially occluded area deserves close study; it is apparent that it cannot be effective in the regional supply, which must be derived from an augmented collateral source.

Sudden Occlusion

This occurs as a plugging of the lumen by solid material—a thrombus or embolus; it is improbable that a sudden swelling of part of the wall effectively obstructs the blood supply in the absence of thrombosis. The grossest parenchymal disturbance will occur when vessels have been previously normal; embolism therefore will produce most extreme change.

Embolism.—Coronary embolism is uncommon, but was observed by Virchow and by Panum (1862). Saphir (1933) recorded a series of 16 cases, and a group of 40 examples was reviewed by Hamman (1941). Embolism may be due to separation of intimal plaques; an embolus thus may contain cholesterol and sometimes calcium salts from an atheromatous lesion (Zak and Elias, 1949), and an example in the coronary artery was described by Moragues, Bawell and Shrader (1950). These lesions cause gross myocardial changes, because a relatively normal vessel is affected suddenly.

Thrombosis.—Platelet deposition and then clotting may completely obstruct the lumen. This should be distinguished from the mural thrombi previously mentioned, though they necessarily merge into each other. Though large thrombi may sometimes occupy the whole lumen, being attached to part of the wall, there is a peripheral crescentic area where blood still flows. The clot may retract, and several channels, by marginal recanalization, probably provide part of the connecting circulation between proximal and distal parts of the vessel (Wright, 1952).

Thrombosis is frequently associated with subintimal hæmorrhage, and is commonly assumed to result from this; but the matter has been incompletely investigated, and the two phenomena are likely to be concomitant rather than causally related (Drury, 1954).

In some cases the thrombus is homogeneous, blood clot predominating, but platelets may be demonstrated. In the small thrombi, however, cells disintegrate and hæmoglobin is removed rapidly; the remaining fibrin is soon replaced by collagenous tissue. Organization with invasion of the clot by fibroblasts and capillaries proceeds as usual, and the surface becomes covered by endothelium. The late crescentic or irregular shape of the lumen may result from one or numerous episodes of thrombosis.

Thrombosis earlier was regarded as being an invariable phenomenon in obstruction, as shown by the term coronary thrombosis. However, it is present in only a proportion of cases, ranging from about 10% (Wright-Smith, 1936) to between 70% and 80% (Saphir *et alii*, 1935; Horn and Finkelstein, 1940). Some investigators have found thrombosis in about 25% (Hallerman, 1939; Moritz and Zamcheck, 1946; Newman, 1946), and others in about 50% (Levine and Brown, 1929; Appelbaum and Nicolson, 1935; French and Dock, 1944). Bjerkelund (1957) reviewed the literature and concluded that a general average would be about 50%.

The discrepancies appear to be due to the different types of cases studied—for example, whether an infarct is present. The time of death after the onset of the condition is of paramount importance; this is well shown in series of coroner's cases, where fewest thrombi are found. If death occurs early, there will not be time for muscle changes to become apparent or for secondary vascular changes to occur. This strongly suggests that thrombosis is often a secondary phenomenon, occurring during the stage of shock and resulting diminution of blood flow. Few attempts have been

made to determine the age of thrombi. It seems that the true figure for the incidence of thrombosis, as the exciting factor in coronary obstruction, should therefore be considerably lower than that observed in the uncritically assessed groups.

Collateral Circulation

Since gross changes occur in arteries without corresponding muscle change, there must be a collateral circulation. This normally is minimal (even though some degree, greater than previously thought, may be present even in youth and in apparently normal hearts), but its development during life is generally recognized. Collateral circulation occurs in two forms, extramyocardial and intramyocardial.

Extramyocardial.—Complete obstruction to both coronary arteries (Redwitz, 1909; Warburg, 1930; King, 1941) demonstrates, in view of the astonishingly good condition of the myocardium, that blood must be supplied by some extra-coronary source. This may occur in two ways.

Extracardiac anastomoses occur between enlarged peripheral branches of the subepicardial coronary vessels in the region of the base of the heart and vessels from the adjacent pericardium, bronchi, etc. (Robertson, 1930, 1935; Warburg, 1930; Hudson, Moritz and Wearn, 1932). Anastomoses with pericardial vessels in adhesions may also be important; advantage has been taken of this and other artificially-induced connexions in surgical procedures to improve the circulation of the heart (Beck, 1955).

Communications between coronary vessels and the cavity of the ventricles, by the Thebesian vessels, have also been regarded as important (Kretz, 1928; Wearn, 1928; Bellet, Gouley and McMillan, 1933; Bohning, Joachim and Katz, 1933).

Intramyocardial. — Communications occur (i) between branches of the two coronary arteries, (ii) between segments of the same vessel, and (iii) between small branches of the same main vessel. These have been demonstrated by injection techniques; the only doubt is regarding their effectiveness. In general, they develop less well in the subendocardial region than elsewhere (Prinzmetal *et alii*, 1948). Clearly, from the lack of correlation between the degree of obstruction and the condition of the myocardium, a significantly functional collateral circulation exists (Blumgart, Schlesinger and Davis, 1940; Snow, Jones and Daber, 1955). At the same time, atherosclerotic or thrombotic changes may outstrip the development of collaterals or involve the vessels from which they receive their blood. A great deal of our knowledge of the collateral circulation and its physiological effectiveness is due to Prinzmetal (Prinzmetal *et alii*, 1942, 1947, 1948).

PATHOGENESIS

Occlusion implies gross obstruction to blood flow, so that failure to find a complete obstruction has always been, not only a matter of astonishment, but also a stimulus to discover the often elusive block. That it is not simply the passage of blood along the vessel, but the amount of oxygen and nutriment arriving at the tissues that is important, has been persistently overlooked. The problem of finding an obstruction, continually emphasized by the dramatically sudden onset of symptoms (even though the age of the infarct is not always related to the clinical history), has applied particularly to cases of massive myocardial infarction.

Sub-Intimal Hæmorrhage

One of the best known postulates was occlusion by sub-intimal hæmorrhage with secondary thrombosis. Although it is not now so important, it attracted attention 20 years ago, and relics of this still remain.

A vascular supply in the vessel wall was known over 100 years ago (Rokitansky, 1841–1846), and vessels in an atheromatous plaque were described by Wolkoff (1929). Similar observations culminated in the beautifully illustrated presentation of Winternitz, Thomas and LeCompte (1938).

Hæmorrhage into the walls of coronary vessels was recognized in the last century (Marie, 1896), and has been described by Boyd (1928) and by Paterson (1936, 1938, 1941), whose suggestion that this could encroach on the lumen of the vessel causing occlusion was supported by Wartman (1938, 1950) and by Horn and Finkelstein (1940). The protrusion of the mass into the lumen was described (Winternitz, Thomas and LeCompte, 1938) and emphasized as causing obstruction to the lumen. The importance of hæmorrhage occurring in degenerate areas and fragility of capillary walls was emphasized by Paterson (1941). Hæmorrhages occur in various parts of the wall (Durlacher *et alii*, 1953), even forming a dissecting aneurysm (LeCount, 1918). Drury (1954) considered that the blood came from the lumen of the artery. Though increased intracapillary pressure has been cited as the cause of the bleeding, it is unlikely even if capillaries communicate with the lumen (King, 1952). Flow through a narrowed area must be

rapid, and consequently the pressure transmitted to such vessels low.

The physical factors involved in distortion of the lumen have been inadequately considered, and misapplied emphasis has been placed on pressure changes, especially with physical effort. The possibility of compression of the lumen was questioned by English and Willius (1943). Intramural hæmorrhage is common, but its significance in vascular obstruction can be appreciated adequately only when physical problems of intimal pressures are considered; it occurs with, rather than initiates, occlusion. Thrombosis sometimes is associated with an intimal hæmorrhage; but these should be regarded as independent complications of atherosclerosis (Drury, 1954).

Spasm

The abrupt onset of symptoms of occlusion has suggested (Leary, 1935*c*) that vascular spasm is responsible. Spasm has been observed directly and demonstrated experimentally in peripheral vessels; it is usually a reflex phenomenon. It has been assumed to account for transient disturbances and generally accepted as the exciting factor in angina pectoris.

Presumably it occurs significantly only in relatively normal vessels. It is not conceivable that thickened, hard or calcified vessels should contract. On the other hand, the occlusive thickening of the intimal wall may be sharply localized to a small area (Schlesinger and Zoll, 1941), and variations in blood supply to a region may depend on changes in more than one part of a vessel or in more than one vessel.

With these reservations in mind, especially that the occluded area of the vessel itself is not necessarily involved, vascular spasm may be significant, not necessarily in causing infarction, but in determining symptoms in some cases (Blumgart, 1947).

"Unexplained" Occlusions

Many cases of myocardial damage (even gross infarction) have been described in which vascular occlusion has not been demonstrated. Even when possible inexperience or carelessness in examination has been rigorously excluded, indubitable examples occur.

These fall into three main classes: (i) arteries are relatively normal; (ii) regional vessels are normal, but adjacent ones recently occluded; (iii) atherosclerosis is obvious locally, but the vessels are patent.

(i) These occlusions occur often in young people without gross disease; commonly there is some general vascular disturbance, and here the concept of coronary insufficiency is important. Physical obstruction to the blood supply is not the important feature, but rather what blood is effectively delivered to the capillaries of the region. The various conditions—shock, anæmia and others grossly lowering the general, and therefore the local, blood pressure—have been discussed by Master and co-workers (1956).

(ii) A collateral circulation, when occlusion of a proximal part of a vessel occurs, allows a continued blood flow through it; but this now comes from some other vessel which has become the main supply to the region (Saphir *et alii*, 1935). If, in due course, this becomes occluded, its relation to the affected myocardial area may not be immediately apparent. This is termed occlusion "at a distance" (Blumgart, Schlesinger and Davis, 1939).

(iii) The suddenness of the onset of symptoms and signs of myocardial involvement always suggests gross recent physical change in the vessel. Often this is not found, and the relative infrequency of thrombosis has been repeatedly noted (Gross and Sternberg, 1939; Friedberg and Horn, 1939; Munck, 1946; Ravin and Geever, 1946; Yu and Stewart, 1950; Horn *et alii*, 1950).

An old occlusion (Blumgart *et alii*, 1950; Littmann and Barr, 1952) may indicate a degree of local circulatory reduction. Then, if a vessel is partially occluded so that its capacity is only that of the minimal needs of the region supplied, a slight further diminution in blood pressure will lower the amount provided below critical requirement.

This is to be correlated with the frequent onset of "occlusion" during rest. Even in cases in which the attack occurs at work, a careful history (obtained before fabrications and pseudo-reminiscences cloud the issue) often shows that it occurred during a rest period. Such is especially important after an active spell, as on sitting down in a public vehicle after walking or running to catch it, sitting down to read the newspaper after working in the garden, and the like. A heavy meal with its mechanical effect on the heart, or a strained position inhibiting venous return (and therefore diminished cardiac output), is known to be important.

The tissue deprivation may occur when the total blood supply is adequate, but oxygen or glucose is inadequate. The importance of anoxia, in general anæmia and pulmonary insufficiency, and of hypoglycæmia (Blotner, 1930; Levy and Bruenn, 1936) has been emphasized. Local anoxia may be determined by fall of blood pressure, as in shock, acute

hæmorrhage (Kohlstaedt and Page, 1944; Master *et alii*, 1950) and exposure to extremes of temperature.

ÆTIOLOGY

The causes of the chronic condition are those of the disease with no special influences except in so far as acute changes are superimposed. In the acute form various additional factors have been proposed.

Stress and Physical Effort

The importance of mechanical factors is usually regarded as self-evident, and worker's compensation has here been an important influence. These may be indirect (already considered with occupation) or direct, ranging from actual trauma to the effect of physical and emotional stresses.

At an earlier period, stress was almost automatically regarded as significant (Fitzhugh and Hamilton, 1933); this was supported by Paterson (1939), even though, including rapidly fatal cases in which changes have been occurring for some time, the activity at the time of death is not relevant (Levy and Bruenn, 1936). No relation between stress and occlusion was found by Luten (1931); attacks of occlusion during sleep were noted by Wolff and White (1926). Phipps (1936) and Stocks (1951) showed that individuals who had had occlusions and returned to work had a better prognosis than those who were sedentary.

An uncritical attitude has been adopted by some observers (Kapp, 1954); a relation to injury should not be claimed in the absence of autopsy examination (Moritz, 1954), and Master and Jaffe (1952) emphasized the care necessary in assessing cases associated with effort.

The times of occurrence of occlusion during the day (Joiner and Kauntze, 1953) indicate their independence of physical activity. The question has been exhaustively reviewed by Master, Dack and Jaffe (1937*a*, 1937*b*, 1939*a*, 1939*b*, 1941) and a lack of correlation of physical effort with attacks of occlusion in most cases has been shown. The acceptance of an association is the easy way as far as insurance cases are concerned, and furthermore, patients like to be told that their condition is due to hard work and conscientiousness rather than to "gluttony or physical indolence" (Arnott, 1954).

Most of the arguments in favour of an association are superficial, and careful review of the clinical features (Master, Dack and Jaffe, 1941), and correlations of pathological findings (Moritz, 1954) or of hæmodynamics (King, 1952) show their fallacy. The significance of less tangible factors is shown by seasonal (winter) incidence (Brown and Pearson, 1948) and a relation to weather changes (Teng and Heyer, 1955). When considered in a general way the relation appears reasonable, but the more carefully the evidence is considered, the less pertinent it becomes.

Relation to Changes in Blood Pressure

A continuously raised diastolic pressure appears statistically to influence the incidence of coronary disease, but its mode of action is not clear; nor is it apparent whether the effect is directly on the arterial wall or merely an indirect association; probably it is the second.

It has often been stated that a sudden rise in pressure will determine an occlusion. This opinion is based on assumptions that this will cause subintimal hæmorrhage. Increased pressure will widen the lumen (Harrison and Wood, 1949; Duguid and Robertson, 1955) and, since there will be a more rapid flow through a partially obstructed region, will not produce subintimal hæmorrhage (King, 1952); nor, with some reservations regarding possible turbulence, will it facilitate thrombosis. More important are the observations of occlusion or coronary insufficiency in conditions of lowered blood pressure (Master *et alii*, 1956).

Relation to Previous Attacks

Although often after an occlusion the individual remains well for years, multiple attacks frequently occur (Boas, 1951; Master *et alii*, 1954; Honey and Truelove, 1957). In view of the universality of atherosclerosis, even though it is patchy, multiple occlusive sites are to be expected, and the single attack emphasizes the greater involvement of some particular vessel. In general, multiple occlusions are the expression of the extent of coronary atherosclerosis.

Post-mortem examination may reveal multiple infarcts distant from each other, showing that they are not necessarily directly related. However, they may be related in two ways; an occlusion may precipitate another distant lesion, or the thrombotic process may spread. At the time of occlusion, gross lowering of blood pressure and liberation of thromboplastin or other factors may facilitate thrombosis elsewhere. This will occur only within a few hours of the original attack. Spread of a thrombus in contiguous vessels may deprive further tissue of its blood supply and thus precipitate further episodes of infarction. This will probably occur within three or four weeks, although it has been stated to take place up to eight weeks

(Snow *et alii*, 1955). After this time, attacks are related only in that they are due to the same arterial disease, and even within that period, the relation must be speculative in the absence of precise autopsy observations.

PART III: THE MYOCARDIUM IN CORONARY DISEASE

IMMEDIATE MYOCARDIAL CHANGES

Many changes occur in heart muscle, ranging from minor physiological disturbances to major dysfunctions associated with demonstrable morphological disorganization.

Pathology

Muscle changes are similar, whether due to diminished blood supply itself or to less oxygen (hypoxia) and glucose (hypoglycæmia). The disturbances, therefore, may be due to either local or general factors. As has already been pointed out, the state of the muscle depends on the relation between the available blood supply and the local demand. Thus, even when a deficiency is of general character, the lesion may be local, because of either anatomical or pathological differences between vessels or variations in demand in different regions.

During life, symptoms (such as pain and shock) may be present in both minor and major incidents. The symptoms will not be considered here; however, sometimes they are either minimal or are overlooked, since evidence of infarction is found *post mortem* in subjects who have not given a clinical history of coronary occlusion (Blumgart, Schlesinger and Davis, 1940; Forbes, 1952).

Macroscopic Characters.—Minor or negligible changes occur, either when the degree of disturbance is too slight to produce morphological alteration in muscle, or when death occurs too early for this to become apparent. The various stages of morphological change are comparable with those seen in infarction elsewhere.

In the first 12 to 24 hours an infarct may be very difficult to recognize. At first, in a region where changes seem inevitable, none is observable. When a few hours elapse between the onset of pain and death, a slightly pale, poorly-defined area is recognizable; at this stage the ventricular wall may bulge slightly—an "acute aneurysm" (Saphir, 1958); after 24 hours the area is softer, drier and paler (grey or greyish-brown) than the surrounding muscle. Hæmorrhage into the tissue is sometimes prominent. That the changes found at death, in either the vessels or the muscle, began some time before must always be considered when their significance is being assessed (Levy and Bruenn, 1936). After two days, yellowish areas appear and extend, so that at about four days the infarct is relatively well defined; a thin, dark-red line demarcates it from surrounding muscle.

In the second week the area, often yellow and friable, is well defined. Invasion by granulation tissue is now progressing, and in three to four weeks (depending on the size of the infarct) organization has occurred. The pinkish granulation tissue gradually changes to grey, and finally to white, firm connective tissue. A fibrinous or serofibrinous pericarditis occurs, with subepicardial lesions and a mural thrombus with subendocardial infarcts.

Infarction occurs most often in the anterior wall and septum (Blumgart, Schlesinger and Davis, 1940; Holyoke, 1945; Ravin and Geever, 1946; Wartman and Hellerstein, 1948; Yater *et alii*, 1948; Snow, Jones and Daber, 1955); though usually involving the ventricular walls including the septum, it may be found in the atria (Cushing *et alii*, 1942; Wartman and Souders, 1950).

Although commonly single, infarcts are sometimes multiple (Wartman and Hellerstein, 1948; Yater *et alii*, 1948). Infarcts of various ages, up to scars, may be found, and extension of an infarct may be associated with extension of a vascular thrombus (Snow, Jones and Daber, 1955).

Infarcts vary in form, and have been classified variously. Attempts to combine different criteria (Sayen, Sheldon and Wolferth, 1955) are likely to be confusing. The site, in relation to the heart, may be anterior, posterior or lateral. or in relation to the walls, subepicardial or subendocardial (Price and James, 1943; Pirani and Schlichter, 1946; Yu and Stewart, 1950; Horn *et alii*, 1950; Master *et alii*, 1956); these may be important electrocardiographically. The stage of the infarct is significant since, once healing has occurred, there will be little or no disturbance of heart action.

In form and distribution, the infarct may be (i) full-thickness, (ii) massive, not full-thickness, (iii) laminar, or (iv) focal (often multiple).

Full-thickness infarcts occur with sudden obstruction of a main coronary vessel. Softening is important at its margins (at the junction with normal muscle), where separation and rupture of the wall take place. Sometimes extensive involvement of part of the wall occurs, but does not affect all layers.

Laminar infarcts have caused most discussion. The similarity in distribution of some old infarcts (scars being more easily delineated) to muscle bundles is striking (Robb, Hiss and Robb, 1935;

Lowe, 1939, 1940; Lowe and Wartman, 1944). That these infarcts represent muscle layers has been criticized, mainly because several vessels supply each muscle (Miale and Bledsoe, 1953), but often only part of a bundle is affected. There is still insufficient evidence for complete assessment, but the more carefully laminar infarcts and scars are studied, the more closely they correspond topographically with parts of muscle layers. Of course, many incomplete, complex or non-laminar scars, which do not fall into any simple anatomical arrangement, are found.

Small focal areas of tissue damage are recognizable as small scattered scars (Buchner and Lucadou, 1943; Grundmann, 1950).

Histological Characters.—Almost immediately after significant diminution in blood supply, changes in the heart muscle begin; at first these are reversible. Experimentally, recovery occurs with up to 20 minutes' occlusion, but after 25 minutes infarction develops (Blumgart, Gilligan and Schlesinger, 1941).

Demonstrable structural change does not occur for six hours after occlusion (Mallory *et alii*, 1939), which may be correlated with experimental "revival" of human hearts up to six hours after death (Kountz, 1936). By this time the fibres begin to stain more deeply, become hyaline and patchily lose their striation. The affected area may be recognized with special histochemical techniques, such as that for succinic dehydrogenase activity (Wachstein and Meisel, 1955). In 24 hours muscle degeneration is becoming obvious; there is polymorphonuclear accumulation, which is gross by the fourth day; organization is occurring at the margin. In the second week macrophages are numerous, and at the end of this week fibrosis begins; collagen formation is prominent in three weeks, and in two months healing is complete. Small infarcts heal more rapidly (four to five weeks) than large ones.

In healed areas, there are fibrosis and "mummified" muscle fibres; some pigment-containing phagocytes occur in groups. Capillaries in these scars are often dilated.

Biochemical Characters.—Apart from succinic dehydrogenase activity, other enzymes in muscle cells will doubtless be employed in due course to demonstrate incipient or overt infarcts. In some organs, notably the pancreas, tissue damage has resulted in escape of enzymes into the blood. In the heart any cellular enzymes, and especially those of the Krebs cycle, may be demonstrable, and some have been observed; glutamic oxalacetic acid transaminase (LaDue *et alii*, 1954; Goble and O'Brien, 1958) has become a recognized clinical adjunct. This is demonstrated by chromatographic and spectrophotometric assay (Nydick *et alii*, 1955, 1957).

Physiological Characters. — General disturbances, such as fever, leucocytosis, hypotension and accelerated sedimentation rate, which occur especially with muscle damage, are prominent. Fall in blood pressure is particularly important, in that it will in turn produce further diminution of blood supply.

Local functional changes are of mechanical and electrical nature. Contractility and conductivity depend on adequate oxygenation and nutrition and, in their absence, may be reduced or lost. Relaxation and stretching of fibres may be an early indication of poor blood supply of either general or local origin.

Electrical changes are specially significant and are well shown in electrocardiograms. In the myocardium there is the normal "current of injury" at the site of damage; it may be considerable and exert far-reaching effects.

When vessels are occluded, spasm may occur, and the sudden change may then cause more extensive changes in the muscle.

Sudden Death.—Cessation of effective heart action occurs as (i) asystole (inhibition of cardiac contraction), (ii) ventricular fibrillation.

Asystole is due to reflex nervous action; but whether the stimulus is determined by sudden anoxia or other stimulus to the nerve or by a current of injury from damaged muscle is still not certainly known.

Ventricular fibrillation, from comparison with experimentally induced conditions, is probably due to electrical stimulation; changes in degree of oxygenation, variations in blood flow and temperature changes may all facilitate its onset. These may occur at the onset of an occlusion or at any time during the destructive and reactive phases of the processes.

Arrhythmias. — These may occur from (i) abnormal foci of stimulation, or (ii) changes in muscle conductivity and excitability.

Stimulation occurs directly from "currents of injury" locally initiated, or reflex nerve stimulation in the affected zone. Apart from muscle damage, the anoxia (local from vascular occlusion or general from hypotension) causes increased excitability of muscle, so that ectopic contractions occur more easily than usual and from small stimuli.

Interference with conductivity may be temporary and functional, or permanent, resulting from structural alterations (with death of muscle and fibrosis). These are most obvious where significantly functional areas, such as the

atrio-ventricular bundle in the septum, are confined to a small space.

Heart Failure.—This may be acute or chronic. Efficient heart action depends on sufficient muscle and its adequate nutrition. When there is loss of much muscle, this may itself impede heart action, the redistribution of the load on the heart wall placing too great a stress on the functioning tissue. As rate of change is important in the effectiveness of stimuli, sudden changes produce correspondingly greater effects. A general fall of blood pressure will influence nutrition and oxygenation, so that cardiac inadequacy may be rapidly progressive, anoxia leading to further diminished muscle efficiency and to still further fall in blood pressure.

The degree of recovery will depend on the patency of the general coronary tree. If constricted or obstructed zones are multiple, then muscle involvement may be widespread, so that recovery does not occur, and the heart will be unable to respond to even slight stresses and will fail or continue to be inefficient.

Recurrent attacks may be more serious than the first, though this will depend on the amount of heart muscle involved in earlier episodes. The amount of any tissue is much in excess of normal requirements, so that even considerable damage may not, as indicated by extensive scars in individuals who have been capable of considerable activity, permanently limit heart action. Therefore, although as a generalization the heart is more susceptible to failure in subsequent attacks, this is neither as great nor as obvious as superficial considerations might suggest.

Rupture—This may be small and superficial, or large, but in either case death is usually due to hæmopericardium. Superficial "rupture" occurs as bleeding from a coronary branch or some dilated vessels at the periphery of an infarct. Occasionally, hæmorrhage in an infarct dissects between muscle layers and may reach the surface. The most characteristic rupture occurs with the full-thickness infarct, usually in the softened layer at the junction of the necrotic and surrounding tissue. It occurs usually about the fifth day.

Pericarditis occurs with subepicardial infarcts; it is not in itself of great significance, but is of clinical value in indicating the site and type of infarction.

Mural thrombi occur particularly with subendocardial infarcts, and are important in the production of emboli in the first days after infarction; however, pulmonary infarcts, probably due to local thrombosis, are more frequent than systemic ones. Anticoagulant therapy is directed towards their control, though without conspicuous success (Feldman *et alii*, 1954).

LATE MYOCARDIAL CHANGES

Chronic myocardial changes, in general, result from widespread arterial disease. Localized lesions may be extensive and lead to rapidly progressive failure; however, if recovery from an attack takes place, provided the remainder of the myocardium has an adequate blood supply, the heart returns to a remarkably normal state. At the same time, involvement of many vessels expedites and accelerates muscle incompetence.

Increase in Heart Size

Although cardiac hypertrophy is found in coronary occlusion, usually when there is hypertension, attempts at correlation are inconclusive, since there are many exceptions. It is important that much of the evidence, clinical or radiographic, will not distinguish between the dilated and hypertrophied heart; indisputable conclusions can be drawn only from direct pathological observations.

The clinical observations are that enlargement of the heart occurs in from 15% to 20% of occlusions, depending on the groups chosen (Master, 1954). Hypertension is found slightly more often in these cases in males, but considerably more often in females. Enlargement is found (even in the absence of hypertension) more commonly after the age of 60 years, when the combination of hypertension and coronary disease, which indicates the aging process, appears to be particularly important.

Histological examination of the heart shows hypertrophied muscle and more connective tissue. Hypertrophy of an individual cell means protoplasmic swelling, but hypertrophy of an organ means increase due to greater size and number of any or all of the components — it does not necessarily imply parenchymal increase alone.

Hypertrophic muscle fibres occur patchily, especially in the neighbourhood of infarcts, in the subendocardial region and often predominantly in one muscle bundle. Some increase of muscle fibres may occur by cell multiplication in the wound (MacMahon, 1937) or by splitting of myocardial fibres (King, 1940), particularly when these are hypertrophied (Linzbach, 1947; Lowe and Bate, 1948; Henschel, 1952). In localized lesions there is increase of connective tissue and fat, and some necrotic muscle cells remain as "mummified" fibres. Altogether there is a volume of tissue

which is functionally ineffective, but which contributes to the weight and size of the organ.

Arteriosclerosis, as opposed to atherosclerosis of the larger arteries, may be responsible for general anoxia, with muscle damage and diffuse fibrosis.

Though there are still uncertainties, tissue increase indubitably occurs in coronary occlusion. Hypertrophy of muscle cells occurs especially in anoxia; the false assumption that an hypertrophied fibre is necessarily better than a normal one is doubtless responsible for much of the scepticism concerning parenchymal hypertrophy in the presence of a defective blood supply. Teleological considerations should be discarded and the matter considered in terms of growth (Grant, 1953), which may occur within certain "physiological" limits, but may become "pathological". It is probably only in the second group that multiplication of fibres, which has been so vehemently denied over the years, takes place. Only when some of the still imperfectly understood fundamental problems associated with hypertrophy and hyperplasia are resolved will the true significance of hypertension and other general factors become intelligible.

Aneurysm

Dilatation of the wall in the acute phase of coronary occlusion has been mentioned as the "acute aneurysm"; recovery of this part of the wall usually occurs.

When a considerable area of wall is affected by a laminar infarct, bulging will occur. With fibrosis and scarring of the area, the pressures within the aneurysmal sac come into equilibrium with mural forces, and further enlargement does not occur (Lowe and Love, 1948). Aneurysms therefore do not rupture and do not themselves necessarily significantly affect heart action; their prognosis is that of a healed comparably sized infarct which has not caused bulging of the wall. Further change is due to progress of the disease and involvement of other parts of the myocardium.

CONCLUSION

In conclusion, recent developments in understanding of the conditions shows that, though only the surface of problems has been scratched, the directions of investigation are clearer; factors controlling metabolic activities are gradually materializing. The many facets of occlusion, especially functional states as insufficiency, are being recognized. These all emphasize the importance of tissue activities rather than complex end results.

It has been possible to review only a small part of an extensive literature; however, the most obvious conclusion from recent work is that considerable progress in understanding of many aspects of coronary disease is being made and should be significant in the next decade.

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